```
Connecting via Winsock to STN



Welcome to STN International!  Enter x:x

LOGINID:ssspta1653hxp

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  JAN 27   Source of Registration (SR) information in REGISTRY updated
                   and searchable
 NEWS  4  JAN 27   A new search aid, the Company Name Thesaurus, available in
                   CA/CAplus
 NEWS  5  FEB 05   German (DE) application and patent publication number format
                   changes
 NEWS  6  MAR 03   MEDLINE and LMEDLINE reloaded
 NEWS  7  MAR 03   MEDLINE file segment of TOXCENTER reloaded
 NEWS  8  MAR 03   FRANCEPAT now available on STN
 NEWS  9  MAR 29   Pharmaceutical Substances (PS) now available on STN
 NEWS 10  MAR 29   WPIFV now available on STN
 NEWS 11  MAR 29   No connect hour charges in WPIFV until May 1, 2004
 NEWS 12  MAR 29   New monthly current-awareness alert (SDI) frequency in RAPRA

 NEWS EXPRESS  MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 13 APRIL 2004
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN Customer
  agreement.  Please note that this agreement limits use to scientific
  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 16:59:27 ON 19 APR 2004

=> file medline, uspatful, dgene, wpids, biosis, fsta, biobusiness
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     1.47       1.47

FILE 'MEDLINE' ENTERED AT 17:03:29 ON 19 APR 2004

FILE 'USPATFULL' ENTERED AT 17:03:29 ON 19 APR 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)
```

FILE 'DGENE' ENTERED AT 17:03:29 ON 19 APR 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE 'WPIDS' ENTERED AT 17:03:29 ON 19 APR 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE 'BIOSIS' ENTERED AT 17:03:29 ON 19 APR 2004
COPYRIGHT (C) 2004 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'FSTA' ENTERED AT 17:03:29 ON 19 APR 2004
COPYRIGHT (C) 2004 International Food Information Service

FILE 'BIOBUSINESS' ENTERED AT 17:03:29 ON 19 APR 2004
COPYRIGHT (C) 2004 Biological Abstracts, Inc. (BIOSIS)

=> ATM or ataxia telangiectasis
ATM IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s ATM or ataxia telangiectasis
L1 93950 ATM OR ATAXIA TELANGIECTASIS

=> s p53
L2 114238 P53

=> s ATR
L3 6648 ATR

=> s l2 and l3
L4 302 L2 AND L3

=> s l4 and inhibit
L5 90 L4 AND INHIBIT

=> s l4 and inhibit interaction
L6 0 L4 AND INHIBIT INTERACTION

=> d l5 ti abs ibib 1-10

L5 ANSWER 1 OF 90 MEDLINE on STN
TI Inhibition of DNA repair by Pentoxifylline and related methylxanthine derivatives.
AB The methylxanthine drug Pentoxifylline is reviewed for new properties which have emerged only relatively recently and for which clinical applications can be expected. After a summary on the established systemic effects of Pentoxifylline on the microcirculation and reduction of tumour anoxia, the role of the drug in the treatment of vasoocclusive disorders, cerebral ischemia, infectious diseases, septic shock and acute respiratory distress, the review focuses on another level of drug action which is based on in vitro observations in a variety of cell lines. Pentoxifylline and the related drug Caffeine are known radiosensitizers especially in **p53** mutant cells. The explanation that the drug abrogates the G2 block and shortens repair in G2 by promoting early entry into mitosis is not anymore tenable because enhancement of radiotoxicity requires presence of the drug during irradiation and fails when the drug is added after irradiation at the G2 maximum. Repair assays by measurement of recovery ratios and by delayed plating experiments indeed strongly suggested a role in repair which is now confirmed for Pentoxifylline by constant field gel electrophoresis (CFGE) measurements and for Pentoxifylline and for Caffeine by use of a variety of repair mutants. The picture now emerging shows that Caffeine and Pentoxifylline **inhibit** homologous recombination by targeting members of the PIK kinase family (ATM and

ATR) which facilitate repair in G2. Pentoxifylline induced repair inhibition between irradiation dose fractions to counter interfraction repair has been successfully applied in a model for stereotactic surgery. Another realistic avenue of application of Pentoxifylline in tumour therapy comes from experiments which show that repair events in G2 can be targeted directly by addition of cytotoxic drugs and Pentoxifylline at the G2 maximum. Under these conditions massive dose enhancement factors of up to 80 have been observed suggesting that it may be possible to realise dramatic improvements to tumour growth control in the clinic.

ACCESSION NUMBER: 2003523173 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14599774
TITLE: Inhibition of DNA repair by Pentoxifylline and related methylxanthine derivatives.
AUTHOR: Bohm Lothar; Roos Wynand Paul; Serafin Antonio Mendes
CORPORATE SOURCE: Department of Pharmacology, Faculty of Health Sciences, University of Stellenbosch, P.O. Box 19063, 7505 Tygerberg, South Africa.. elb@sun.ac.za
SOURCE: Toxicology, (2003 Nov 15) 193 (1-2) 153-60. Ref: 72
Journal code: 0361055. ISSN: 0300-483X.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 20031106
Last Updated on STN: 20031217
Entered Medline: 20031216

L5 ANSWER 2 OF 90 MEDLINE on STN
TI Cisplatin: mode of cytotoxic action and molecular basis of resistance.
AB Cisplatin is one of the most potent antitumor agents known, displaying clinical activity against a wide variety of solid tumors. Its cytotoxic mode of action is mediated by its interaction with DNA to form DNA adducts, primarily intrastrand crosslink adducts, which activate several signal transduction pathways, including those involving **ATR**, **p53**, p73, and MAPK, and culminate in the activation of apoptosis. DNA damage-mediated apoptotic signals, however, can be attenuated, and the resistance that ensues is a major limitation of cisplatin-based chemotherapy. The mechanisms responsible for cisplatin resistance are several, and contribute to the multifactorial nature of the problem. Resistance mechanisms that limit the extent of DNA damage include reduced drug uptake, increased drug inactivation, and increased DNA adduct repair. Origins of these pharmacologic-based mechanisms, however, are at the molecular level. Mechanisms that **inhibit** propagation of the DNA damage signal to the apoptotic machinery include loss of damage recognition, overexpression of HER-2/neu, activation of the PI3-K/Akt (also known as PI3-K/PKB) pathway, loss of **p53** function, overexpression of antiapoptotic bcl-2, and interference in caspase activation. The molecular signature defining the resistant phenotype varies between tumors, and the number of resistance mechanisms activated in response to selection pressures dictates the overall extent of cisplatin resistance.

ACCESSION NUMBER: 2003499403 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14576837
TITLE: Cisplatin: mode of cytotoxic action and molecular basis of resistance.
AUTHOR: Siddik Zahid H
CORPORATE SOURCE: Department of Experimental Therapeutics, Unit 104, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030-4009, USA.. zsiddik@mdanderson.org
CONTRACT NUMBER: CA 77332 (NCI)

CA 82361 (NCI)
SOURCE: Oncogene, (2003 Oct 20) 22 (47) 7265-79. Ref: 225
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200311
ENTRY DATE: Entered STN: 20031025
Last Updated on STN: 20031219
Entered Medline: 20031121

L5 ANSWER 3 OF 90 MEDLINE on STN
TI DNA damage checkpoint control in cells exposed to ionizing radiation.
AB Damage induced in the DNA after exposure of cells to ionizing radiation activates checkpoint pathways that **inhibit** progression of cells through the G1 and G2 phases and induce a transient delay in the progression through S phase. Checkpoints together with repair and apoptosis are integrated in a circuitry that determines the ultimate response of a cell to DNA damage. Checkpoint activation typically requires sensors and mediators of DNA damage, signal transducers and effectors. Here, we review the current state of knowledge regarding mechanisms of checkpoint activation and proteins involved in the different steps of the process. Emphasis is placed on the role of ATM and **ATR**, as well on CHK1 and CHK2 kinases in checkpoint response. The roles of downstream effectors, such as **P53** and the CDC25 family of proteins, are also described, and connections between repair and checkpoint activation are attempted. The role of checkpoints in genomic stability and the potential of improving the treatment of cancer by DNA damage inducing agents through checkpoint abrogation are also briefly outlined.
ACCESSION NUMBER: 2003408354 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12947390
TITLE: DNA damage checkpoint control in cells exposed to ionizing radiation.
AUTHOR: Iliakis George; Wang Ya; Guan Jun; Wang Huichen
CORPORATE SOURCE: Institute of Medical Radiation Biology, University of Essen Medical School, Hufelanstrasse 55, 45122 Essen, Germany.. Georg.Iliakis@uni-essen.de
CONTRACT NUMBER: 2P01 CA56690 (NCI)
CA42026 (NCI)
CA56706 (NCI)
CA76203 (NCI)
SOURCE: Oncogene, (2003 Sep 1) 22 (37) 5834-47.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030830
Last Updated on STN: 20031002
Entered Medline: 20031001

L5 ANSWER 4 OF 90 MEDLINE on STN
TI Protein kinase inhibitor 2-aminopurine overrides multiple genotoxic stress-induced cellular pathways to promote cell survival.
AB 2-Aminopurine (2-AP) is an adenine analog shown to cause cells to bypass chemical- and radiation-induced cell cycle arrest through as-yet unidentified mechanisms. 2-AP has also been shown to act as a kinase inhibitor. Tumor suppressor **p53** plays an important role in the control of cell cycle and apoptosis in response to genotoxic stress. We

were interested in examining the effect of 2-AP on **p53** phosphorylation and its possible consequences on checkpoint control in cells subjected to various forms of DNA damage. Here, we show that 2-AP suppresses **p53** phosphorylation in response to gamma radiation, adriamycin, or ultraviolet treatment. This is partly explained by the ability of the kinase inhibitor to **inhibit** ATM or **ATR** activities in vitro and impair ATM- or **ATR**-dependent **p53** phosphorylation in vivo. However, 2-AP is also capable of inhibiting **p53** phosphorylation in cells deficient in ATM, DNA-PK, or **ATR** suggesting the existence of multiple pathways by which this kinase inhibitor modulates **p53** activation. Biologically, the 2-AP-mediated inhibition of **p53** stabilization enables wild-type **p53**-containing cells to bypass adriamycin-induced G(2)/M arrest. In the long term, however, 2-AP facilitates cells to resist DNA damage-induced cell death independently of **p53**.

ACCESSION NUMBER: 2003275742 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12802279
TITLE: Protein kinase inhibitor 2-aminopurine overrides multiple genotoxic stress-induced cellular pathways to promote cell survival.
AUTHOR: Huang Shirley; Qu Li-Ke; Cuddihy Andrew R; Ragheb Rafik; Taya Yoichi; Koromilas Antonis E
CORPORATE SOURCE: Department of Microbiology and Immunology, McGill University, Montreal, Canada H3A 2T5.
SOURCE: Oncogene, (2003 Jun 12) 22 (24) 3721-33. Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030613
Last Updated on STN: 20030703
Entered Medline: 20030702

L5 ANSWER 5 OF 90 MEDLINE on STN
TI G2 DNA damage checkpoint inhibition and antimitotic activity of 13-hydroxy-15-oxozoapatlin.
AB Checkpoints activated in response to DNA damage cause arrest in the G(1) and G(2) phases of the cell cycle. Inhibitors of the G(2) checkpoint may be used as tools to study this response and also to increase the effectiveness of DNA-damaging therapies against cancers lacking **p53** function. Using a cell-based assay for G(2) checkpoint inhibitors, we have screened extracts from the NCI National Institutes of Health Natural Products Repository and have identified 13-hydroxy-15-oxozoapatlin (OZ) from the African tree Parinari curatellifolia. Flow cytometry with a mitosis-specific antibody showed that checkpoint inhibition by OZ was maximal at 10 microm, which released 20% of irradiated MCF-7 cells expressing defective **p53** and 30% of irradiated HCT116p53(-/-) cells from G(2) arrest. OZ additively increased the response to the checkpoint inhibitors isogranulatimide and debromohymenialdisine, but it did not augment the effects of UCN-01 or caffeine. Unlike other checkpoint inhibitors, OZ did not **inhibit** ataxia-telangiectasia mutated (ATM), ATM and Rad3-related (**ATR**), Chk1, Chk2, Plk1, or Ser/Thr protein phosphatases in vitro. Treatment with OZ also caused G(2)-arrested and cycling cells to arrest in mitosis in a state resembling prometaphase. In these cells, the chromosomes were condensed and scattered over disordered mitotic spindles. The results demonstrate that OZ is both a G(2) checkpoint inhibitor and an antimitotic agent.

ACCESSION NUMBER: 2002046807 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11572854
TITLE: G2 DNA damage checkpoint inhibition and antimitotic activity of 13-hydroxy-15-oxozoapatlin.

AUTHOR: Rundle N T; Xu L; Andersen R J; Roberge M
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of British Columbia, Vancouver, British Columbia V6T 1Z3, Canada.
SOURCE: Journal of biological chemistry, (2001 Dec 21) 276 (51) 48231-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20030105
Entered Medline: 20020131

L5 ANSWER 6 OF 90 MEDLINE on STN
TI **ATR** inhibition selectively sensitizes G1 checkpoint-deficient cells to lethal premature chromatin condensation.
AB Premature chromatin condensation (PCC) is a hallmark of mammalian cells that begin mitosis before completing DNA replication. This lethal event is prevented by a highly conserved checkpoint involving an unknown, caffeine-sensitive mediator. Here, we have examined the possible involvement of the caffeine-sensitive ATM and **ATR** protein kinases in this checkpoint. We show that caffeine's ability to **inhibit ATR** (but not ATM) causes PCC, that **ATR** (but not ATM) prevents PCC, and that **ATR** prevents PCC via Chk-1 regulation. Moreover, mimicking cancer cell phenotypes by disrupting normal G(1) checkpoints sensitizes cells to PCC by **ATR** inhibition plus low-dose DNA damage. Notably, loss of **p53** function potently sensitizes cells to PCC caused by **ATR** inhibition by a small molecule. We present a molecular model for how **ATR** prevents PCC and suggest that **ATR** represents an attractive therapeutic target for selectively killing cancer cells by premature chromatin condensation.
ACCESSION NUMBER: 2001445854 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11481475
TITLE: **ATR** inhibition selectively sensitizes G1 checkpoint-deficient cells to lethal premature chromatin condensation.
AUTHOR: Nghiem P; Park P K; Kim Y; Vaziri C; Schreiber S L
CORPORATE SOURCE: Department of Chemistry and Chemical Biology, Howard Hughes Medical Institute, Harvard University, Cambridge, MA 02138, USA.
CONTRACT NUMBER: GM-52067 (NIGMS)
K08-AR0208703 (NIAMS)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2001 Jul 31) 98 (16) 9092-7.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010903
Entered Medline: 20010830

L5 ANSWER 7 OF 90 MEDLINE on STN
TI Regulation of the G2/M transition by **p53**.
AB **p53** protects mammals from neoplasia by inducing apoptosis, DNA repair and cell cycle arrest in response to a variety of stresses. **p53**-dependent arrest of cells in the G1 phase of the cell cycle is an important component of the cellular response to stress. Here we review

recent evidence that implicates **p53** in controlling entry into mitosis when cells enter G2 with damaged DNA or when they are arrested in S phase due to depletion of the substrates required for DNA synthesis. Part of the mechanism by which **p53** blocks cells at the G2 checkpoint involves inhibition of Cdc2, the cyclin-dependent kinase required to enter mitosis. Cdc2 is inhibited simultaneously by three transcriptional targets of **p53**, Gadd45, p21, and 14-3-3 sigma. Binding of Cdc2 to Cyclin B1 is required for its activity, and repression of the cyclin B1 gene by **p53** also contributes to blocking entry into mitosis. **p53** also represses the cdc2 gene, to help ensure that cells do not escape the initial block. Genotoxic stress also activates **p53**-independent pathways that **inhibit** Cdc2 activity, activation of the protein kinases Chk1 and Chk2 by the protein kinases Atm and **Atr**. Chk1 and Chk2 **inhibit** Cdc2 by inactivating Cdc25, the phosphatase that normally activates Cdc2. Chk1, Chk2, Atm and **Atr** also contribute to the activation of **p53** in response to genotoxic stress and therefore play multiple roles. **p53** induces transcription of the reprimo, B99, and mcg10 genes, all of which contribute to the arrest of cells in G2, but the mechanisms of cell cycle arrest by these genes is not known. Repression of the topoisomerase II gene by **p53** helps to block entry into mitosis and strengthens the G2 arrest. In summary, multiple overlapping **p53**-dependent and **p53**-independent pathways regulate the G2/M transition in response to genotoxic stress.

ACCESSION NUMBER: 2001237339 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11313928
TITLE: Regulation of the G2/M transition by **p53**.
AUTHOR: Taylor W R; Stark G R
CORPORATE SOURCE: Department of Molecular Biology, Lerner Research Insititute, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA.
CONTRACT NUMBER: GM49345 (NIGMS)
SOURCE: Oncogene, (2001 Apr 5) 20 (15) 1803-15. Ref: 126
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010503

L5 ANSWER 8 OF 90 MEDLINE on STN
TI Inhibition of ATM and **ATR** kinase activities by the radiosensitizing agent, caffeine.
AB Caffeine exposure sensitizes tumor cells to ionizing radiation and other genotoxic agents. The radiosensitizing effects of caffeine are associated with the disruption of multiple DNA damage-responsive cell cycle checkpoints. The similarity of these checkpoint defects to those seen in ataxia-telangiectasia (A-T) suggested that caffeine might **inhibit** one or more components in an A-T mutated (ATM)-dependent checkpoint pathway in DNA-damaged cells. We now show that caffeine inhibits the catalytic activity of both ATM and the related kinase, ATM and Rad3-related (**ATR**), at drug concentrations similar to those that induce radiosensitization. Moreover, like ATM-deficient cells, caffeine-treated A549 lung carcinoma cells irradiated in G2 fail to arrest progression into mitosis, and S-phase-irradiated cells exhibit radioresistant DNA synthesis. Similar concentrations of caffeine also **inhibit** gamma- and UV radiation-induced phosphorylation of **p53** on Ser15, a modification that may be directly mediated by the ATM and **ATR** kinases. DNA-dependent protein kinase, another

ATM-related protein involved in DNA damage repair, was resistant to the inhibitory effects of caffeine. Likewise, the catalytic activity of the G2 checkpoint kinase, hChk1, was only marginally suppressed by caffeine but was inhibited potently by the structurally distinct radiosensitizer, UCN-01. These data suggest that the radiosensitizing effects of caffeine are related to inhibition of the protein kinase activities of ATM and **ATR** and that both proteins are relevant targets for the development of novel anticancer agents.

ACCESSION NUMBER: 1999413496 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10485486
TITLE: Inhibition of ATM and **ATR** kinase activities by the radiosensitizing agent, caffeine.
AUTHOR: Sarkaria J N; Busby E C; Tibbetts R S; Roos P; Taya Y; Karnitz L M; Abraham R T
CORPORATE SOURCE: Division of Oncology Research, Mayo Clinic, Rochester, Minnesota 55905, USA.. sarkaria.jann@mayo.edu
CONTRACT NUMBER: CA52995 (NCI)
CA69709 (NCI)
CA76193 (NCI)
+
SOURCE: Cancer research, (1999 Sep 1) 59 (17) 4375-82.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991012
Last Updated on STN: 20020420
Entered Medline: 19990930

L5 ANSWER 9 OF 90 MEDLINE on STN
TI Cleavage and inactivation of ATM during apoptosis.
AB The activation of the cysteine proteases with aspartate specificity, termed caspases, is of fundamental importance for the execution of programmed cell death. These proteases are highly specific in their action and activate or **inhibit** a variety of key protein molecules in the cell. Here, we study the effect of apoptosis on the integrity of two proteins that have critical roles in DNA damage signalling, cell cycle checkpoint controls, and genome maintenance-the product of the gene defective in ataxia telangiectasia, ATM, and the related protein **ATR**. We find that ATM but not **ATR** is specifically cleaved in cells induced to undergo apoptosis by a variety of stimuli. We establish that ATM cleavage in vivo is dependent on caspases, reveal that ATM is an efficient substrate for caspase 3 but not caspase 6 in vitro, and show that the in vitro caspase 3 cleavage pattern mirrors that in cells undergoing apoptosis. Strikingly, apoptotic cleavage of ATM in vivo abrogates its protein kinase activity against **p53** but has no apparent effect on the DNA binding properties of ATM. These data suggest that the cleavage of ATM during apoptosis generates a kinase-inactive protein that acts, through its DNA binding ability, in a trans-dominant-negative fashion to prevent DNA repair and DNA damage signalling.

ACCESSION NUMBER: 1999384276 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10454555
TITLE: Cleavage and inactivation of ATM during apoptosis.
AUTHOR: Smith G C; d'Adda di Fagagna F; Lakin N D; Jackson S P
CORPORATE SOURCE: Wellcome/CRC Institute and Department of Zoology, University of Cambridge, Cambridge, United Kingdom.
SOURCE: Molecular and cellular biology, (1999 Sep) 19 (9) 6076-84.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19990925
Last Updated on STN: 20020221
Entered Medline: 19990910

L5 ANSWER 10 OF 90 USPATFULL on STN

TI Mechanism of mitochondrial membrane permeabilization by HIV-1 Vpr, mimetics of Vpr and methods of screening active molecules having the ability to alter and/or prevent and/or mimic the interaction of Vpr with ANT

AB The invention is directed to the induction of mitochondrial membrane permeabilization via the physical and functional interaction of the HIV-1 Vpr protein with the mitochondrial inner membrane protein ANT (adenine nucleotide translocator, also called adenine nucleotide translocase or ADP/ATP carrier). Reagents and methods for inducing and/or inhibiting the binding of Vpr to ANT, mitochondrial membrane permeabilization, and apoptosis are provided.

ACCESSION NUMBER: 2004:94694 USPATFULL
TITLE: Mechanism of mitochondrial membrane permeabilization by HIV-1 Vpr, mimetics of Vpr and methods of screening active molecules having the ability to alter and/or prevent and/or mimic the interaction of Vpr with ANT
INVENTOR(S): Jacotot, Etienne Daniel Francois, Paris, FRANCE
Kroemer, Guido, Paris, FRANCE
Roques, Bernard Pierre, Paris, FRANCE
Edelmann, Lena, Boulogne, FRANCE
Hoebeke, Johan, Schiltighcim, FRANCE
Brenner-Jan, Catherine, LeChesnay, FRANCE
Belzacq, Anne-Sophie, Paris, FRANCE

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004072146	A1	20040415
APPLICATION INFO.:	US 2003-383592	A1	20030310 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. WO 2001-EP11316, filed on 11 Sep 2001, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-231539P	20000911 (60)
	US 2000-232841P	20000915 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Finnegan, Henderson, Farabow,, Garrett & Dunner, L.L.P., 1300 I Street, N.W., Washington, DC, 20005-3315
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 16 Drawing Page(s)
LINE COUNT: 1682

=> d his

(FILE 'HOME' ENTERED AT 16:59:27 ON 19 APR 2004)

FILE 'MEDLINE, USPATFULL, DGENE, WPIDS, BIOSIS, FSTA, BIOBUSINESS'
ENTERED AT 17:03:29 ON 19 APR 2004
L1 93950 S ATM OR ATAXIA TELANGIECTASIS
L2 114238 S P53
L3 6648 S ATR
L4 302 S L2 AND L3
L5 90 S L4 AND INHIBIT

```
L6            0 S L4 AND INHIBIT INTERACTION

=> s l5 and compound
L7            64 L5 AND COMPOUND

=> s l7 and peptide
L8            59 L7 AND PEPTIDE

=> d l8 ti abs ibib 1-10

L8   ANSWER 1 OF 59  USPATFULL on STN
TI     Mechanism of mitochondrial membrane permeabilization by HIV-1 Vpr,
       mimetics of Vpr and methods of screening active molecules having the
       ability to alter and/or prevent and/or mimic the interaction of Vpr with
       ANT
AB     The invention is directed to the induction of mitochondrial membrane
       permeabilization via the physical and functional interaction of the
       HIV-1 Vpr protein with the mitochondrial inner membrane protein ANT
       (adenine nucleotide translocator, also called adenine nucleotide
       translocase or ADP/ATP carrier). Reagents and methods for inducing
       and/or inhibiting the binding of Vpr to ANT, mitochondrial membrane
       permeabilization, and apoptosis are provided.

ACCESSION NUMBER:        2004:94694  USPATFULL
TITLE:                   Mechanism of mitochondrial membrane permeabilization by
                         HIV-1 Vpr, mimetics of Vpr and methods of screening
                         active molecules having the ability to alter and/or
                         prevent and/or mimic the interaction of Vpr with ANT
INVENTOR(S):             Jacotot, Etienne Daniel Francois, Paris, FRANCE
                         Kroemer, Guido, Paris, FRANCE
                         Roques, Bernard Pierre, Paris, FRANCE
                         Edelmann, Lena, Boulogne, FRANCE
                         Hoebeke, Johan, Schiltighcim, FRANCE
                         Brenner-Jan, Catherine, LeChesnay, FRANCE
                         Belzacq, Anne-Sophie, Paris, FRANCE

                              NUMBER        KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 2004072146      A1   20040415
APPLICATION INFO.:       US 2003-383592     A1   20030310  (10)
RELATED APPLN. INFO.:    Continuation of Ser. No. WO 2001-EP11316, filed on 11
                         Sep 2001, UNKNOWN

                                NUMBER         DATE
                         ------------------ --------
PRIORITY INFORMATION:    US 2000-231539P    20000911 (60)
                         US 2000-232841P    20000915 (60)
DOCUMENT TYPE:           Utility
FILE SEGMENT:            APPLICATION
LEGAL REPRESENTATIVE:    Finnegan, Henderson, Farabow,, Garrett & Dunner,
                         L.L.P., 1300 I Street, N.W., Washington, DC, 20005-3315
NUMBER OF CLAIMS:        23
EXEMPLARY CLAIM:         1
NUMBER OF DRAWINGS:      16 Drawing Page(s)
LINE COUNT:              1682

L8   ANSWER 2 OF 59  USPATFULL on STN
TI     Novel proteases
AB     The present invention relates to protease polypeptides, nucleotide
       sequences encoding the protease polypeptides, as well as various
       products and methods useful for the diagnosis and treatment of various
       protease-related diseases and conditions. Through the use of a
       bioinformatics strategy, mammalian members of the of PTK's and STK's
       have been identified and their protein structure predicted.
```

ACCESSION NUMBER: 2004:82657 USPATFULL
TITLE: Novel proteases
INVENTOR(S): Plowman, Gregory D., San Carlos, CA, UNITED STATES
Whyte, David, Belmont, CA, UNITED STATES
Sudarsanam, Sucha, Greenbrae, CA, UNITED STATES
Manning, Gerard, Menlo Park, CA, UNITED STATES
Caenepeel, Sean R., Oakland, CA, UNITED STATES
Payne, Vilia A., Chesterfield, MO, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004063107	A1	20040401
APPLICATION INFO.:	US 2003-275107	A1	20030320 (10)
	WO 2001-US14431		20010504

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FOLEY AND LARDNER, SUITE 500, 3000 K STREET NW, WASHINGTON, DC, 20007
NUMBER OF CLAIMS: 28
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 32 Drawing Page(s)
LINE COUNT: 11804

L8 ANSWER 3 OF 59 USPATFULL on STN
TI 14171 Protein kinase, a novel human protein kinase and uses thereof
AB The invention relates to a novel kinase nucleic acid sequence and protein. Also provided are vectors, host cells, and recombinant methods for making and using the novel molecules.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2004:63787 USPATFULL
TITLE: 14171 Protein kinase, a novel human protein kinase and uses thereof
INVENTOR(S): Kapeller-Libermann, Rosana, Chestnut Hill, MA, UNITED STATES
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004048305	A1	20040311
APPLICATION INFO.:	US 2003-658904	A1	20030910 (10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2001-781882, filed on 12 Feb 2001, GRANTED, Pat. No. US 6630335		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-182096P	20000211 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MILLENNIUM PHARMACEUTICALS, INC., 40 Landsdowne Street, CAMBRIDGE, MA, 02139
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 5414
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 4 OF 59 USPATFULL on STN
TI Drug screening systems and assays
AB A method of stimulating non-homologous end-joining (NHEJ) of DNA the method comprising performing NHEJ of DNA in the presence of inositol hexakisphosphate (IP.sub.6) or other stimulatory inositol phosphate. An assay of a protein kinase wherein the assay comprises inositol

hexakisphosphate (IP.sub.6) or other stimulatory inositol phosphate. The invention also provides screening assays for compounds which may modulate NHEJ and which may be therapeutically useful; and screening assays for compounds which may modulate DNA-PK and related protein kinases and which may be therapeutically useful. Methods of modulating NHEJ and protein kinases are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2004:38591 USPATFULL			
TITLE:	Drug screening systems and assays			
INVENTOR(S):	West, Steve Craig, South Mimms Hertfordshire, UNITED KINGDOM Bartlett-Jones, Michael, London, UNITED KINGDOM Akemi Hanakahi, Leslyn Ann, Baltimore, MD, UNITED STATES			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004029130	A1	20040212	
APPLICATION INFO.:	US 2003-296014	A1	20030612	(10)
	WO 2001-GB2180		20010518	
	NUMBER		DATE	
PRIORITY INFORMATION:	GB 2000-12179		20000520	
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
LEGAL REPRESENTATIVE:	FISH & RICHARDSON PC, 225 FRANKLIN ST, BOSTON, MA, 02110			
NUMBER OF CLAIMS:	56			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	18 Drawing Page(s)			
LINE COUNT:	2260			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 5 OF 59 USPATFULL on STN

TI Methods for detecting dna damage and screening for cancer therapeutics

AB A method for detecting DNA damage in a tissue sample involves contacting an immobilized biological sample with a labeled ligand which binds to human 53Bp1, and examining the immobilized sample for the presence of a label generated-detectable signal concentrated in foci in said sample. The presence of concentrated foci is indicative of DNA damage and the presence of diffuse signal is indicative of a normal sample. Diagnostic reagents contain a ligand that binds to human 53Bp1 associated with a detectable label. Diagnostic kits for detecting DNA damage in a biological sample contain such diagnostic reagents and signal detection components. Compositions that **inhibit** or antagonize the biological activity of 53Bp1 are identified by suitable assays, and are employed in methods of retarding the growth of a cancer cell.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2004:31097 USPATFULL			
TITLE:	Methods for detecting dna damage and screening for cancer therapeutics			
INVENTOR(S):	Halazonetis, Thanos, Wynnewood, PA, UNITED STATES Schultz, Linda B., Suwanee, GA, UNITED STATES			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004023235	A1	20040205	
APPLICATION INFO.:	US 2003-276312	A1	20030117	(10)
	WO 2001-US17471		20010530	
	NUMBER		DATE	

PRIORITY INFORMATION:	US 2000-60208716	20000601
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	HOWSON AND HOWSON, ONE SPRING HOUSE CORPORATION CENTER, BOX 457, 321 NORRISTOWN ROAD, SPRING HOUSE, PA, 19477	
NUMBER OF CLAIMS:	31	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	2 Drawing Page(s)	
LINE COUNT:	2295	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 6 OF 59 USPATFULL on STN

TI Compositions, kits, and methods for identification, assessment, prevention, and therapy of human prostate cancer

AB The invention relates to compositions, kits, and methods for diagnosing, staging, prognosing, monitoring and treating human prostate cancers. A variety of marker genes are provided, wherein changes in the levels of expression of one or more of the marker genes is correlated with the presence of prostate cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2004:12961 USPATFULL		
TITLE:	Compositions, kits, and methods for identification, assessment, prevention, and therapy of human prostate cancer		
INVENTOR(S):	Schlegel, Robert, Auburndale, MA, UNITED STATES Endege, Wilson O., Norwood, MA, UNITED STATES		
PATENT ASSIGNEE(S):	Millennium Pharmaceuticals, Inc., Cambridge, MA (U.S. corporation)		

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004009481	A1	20040115	
APPLICATION INFO.:	US 2002-166883	A1	20020611	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2001-297285P	20010611	(60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	LAHIVE & COCKFIELD, 28 STATE STREET, BOSTON, MA, 02109
NUMBER OF CLAIMS:	27
EXEMPLARY CLAIM:	1
LINE COUNT:	15572

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 7 OF 59 USPATFULL on STN

TI SIR2 activity

AB This invention relates to methods of screening compounds that modulate cellular and organismal processes by modification of the activity of SIR2 and/or transcription factors, e.g., **p53**, particularly methods of screening for compounds that modify lifespan and/or metabolism of a cell or an organism by modulation of the activity of SIR2 and/or transcription factors, e.g., **p53**, and more particularly to methods of screening for compounds that modulate the activity of Sir2 and/or transcription factors, e.g., **p53**. In particular, the present invention relates to a method for screening a **compound**, by providing a test mixture comprising a transcription factor, Sir2, and a Sir2 cofactor with the **compound**, and evaluating an activity of a component of the test mixture in the presence of the **compound**. The invention further relates to therapeutic uses of said compounds. The invention further relates to a method of modifying the acetylation status of a transcription factor

binding site on histone or DNA by raising local concentrations of Sir2.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2004:7340 USPATFULL
TITLE:	SIR2 activity
INVENTOR(S):	Guarente, Leonard, Chestnut Hill, MA, UNITED STATES Vaziri, Homayoun, Thornhill, CANADA Imai, Shin-Ichiro, St. Louis, MO, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004005574	A1	20040108
APPLICATION INFO.:	US 2002-191121	A1	20020708 (10)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	FISH & RICHARDSON PC, 225 FRANKLIN ST, BOSTON, MA, 02110
NUMBER OF CLAIMS:	41
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	32 Drawing Page(s)
LINE COUNT:	4559

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 8 OF 59 USPATFULL on STN

TI Methods of diagnosis of ovarian cancer, compositions and methods of screening for modulators of ovarian cancer

AB Described herein are genes whose expression are up-regulated or down-regulated in ovarian cancer. Related methods and compositions that can be used for diagnosis and treatment of ovarian cancer are disclosed. Also described herein are methods that can be used to identify modulators of ovarian cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2004:7329 USPATFULL
TITLE:	Methods of diagnosis of ovarian cancer, compositions and methods of screening for modulators of ovarian cancer
INVENTOR(S):	Mack, David H., Menlo Park, CA, UNITED STATES Gish, Kurt C., San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S):	Eos Biotechnology, Inc., South San Francisco, CA (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004005563	A1	20040108
APPLICATION INFO.:	US 2002-173999	A1	20020617 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-372246P	20020412 (60)
	US 2001-350666P	20011113 (60)
	US 2001-315287P	20010827 (60)
	US 2001-299234P	20010618 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834
NUMBER OF CLAIMS:	24
EXEMPLARY CLAIM:	1
LINE COUNT:	32540

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 9 OF 59 USPATFULL on STN

TI Catalytic domain of the human effector cell cycle checkpoint protein

kinase materials and methods for identification of inhibitors thereof

AB The present invention relates to the identification, isolation and purification of the catalytic domain of the human effector checkpoint protein kinase (hChk1). A 1.7Å crystal structure of the hChk1 kinase domain in the active conformation is reported herein. The kinase domain of hChk1 and its associated crystal structure is described for use in the discovery, identification and characterization of inhibitors of hChk1. This structure provides a three-dimensional description of the binding site of the hChk1 for structure-based design of small molecule inhibitors thereof as therapeutic agents. Inhibitors of hChk1 find utility in the treatment of hyperproliferative disorders such as HIV and cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2003:337218 USPATFULL
TITLE:	Catalytic domain of the human effector cell cycle checkpoint protein kinase materials and methods for identification of inhibitors thereof
INVENTOR(S):	Chen, Ping, San Diego, CA, United States Anderson, Mark, San Diego, CA, United States Deng, Ya-Li, San Diego, CA, United States Gaur, Smita, San Diego, CA, United States Kan, Chen Chen, Arcadia, CA, United States Luo, Chun, San Diego, CA, United States Lundgren, Karen, San Diego, CA, United States Margosiak, Stephen, Escondido, CA, United States Nguyen, Binh, San Diego, CA, United States O'Connor, Patrick, San Diego, CA, United States Register, James, San Diego, CA, United States Russell, Anna Tempczyk, San Diego, CA, United States Sarup, Jay, San Diego, CA, United States
PATENT ASSIGNEE(S):	Agouron Pharmaceuticals, Inc., San Diego, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6670167	B1	20031230	
APPLICATION INFO.:	US 1999-460421		19991214	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-162887P	19991101 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Prouty, Rebecca E.
ASSISTANT EXAMINER:	Steadman, David
LEGAL REPRESENTATIVE:	Djuardi, Elsa, Zielinski, Bryan C., Richardson, Peter C.
NUMBER OF CLAIMS:	17
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	126 Drawing Figure(s); 126 Drawing Page(s)
LINE COUNT:	2702

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 10 OF 59 USPATFULL on STN

TI Catalytic domain of the human effector cell cycle checkpoint protein kinase Chk1 materials and methods for identification of inhibitors thereof

AB The present invention relates to the identification, isolation and purification of the catalytic domain of the human effector checkpoint protein kinase (hChk1). A 1.7 Å crystal structure of the hChk1 kinase domain in the active conformation is reported herein. The kinase domain of hChk1 and its associated crystal structure is described for use in the discovery, identification and characterization of inhibitors

of hChk1. This structure provides a three-dimensional description of the binding site of the hChk1 for structure-based design of small molecule inhibitors thereof as therapeutic agents. Inhibitors of hChk1 find utility in the treatment of hyperproliferative disorders such as HIV and cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2003:335023 USPATFULL
TITLE:	Catalytic domain of the human effector cell cycle checkpoint protein kinase Chk1 materials and methods for identification of inhibitors thereof
INVENTOR(S):	Chen, Ping, San Diego, CA, UNITED STATES Anderson, Mark, San Diego, CA, UNITED STATES Deng, Ya-Li, San Diego, CA, UNITED STATES Gaur, Smita, San Diego, CA, UNITED STATES Kan, Chen Chen, Arcadia, CA, UNITED STATES Luo, Chun, San Diego, CA, UNITED STATES Lundgren, Karen, San Diego, CA, UNITED STATES Margosiak, Stephen, Escondido, CA, UNITED STATES Nguyen, Binh, San Diego, CA, UNITED STATES O'Connor, Patrick, San Diego, CA, UNITED STATES Reqister, James, San Diego, CA, UNITED STATES Russell, Anna Tempczyk, San Diego, CA, UNITED STATES Sarup, Jay, San Diego, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003235899	A1	20031225
APPLICATION INFO.:	US 2003-353274	A1	20030128 (10)
RELATED APPLN. INFO.:	Division of Ser. No. US 1999-460421, filed on 14 Dec 1999, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-162887P	19991101 (60)
	US 1999-152196P	19990901 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	AGOURON PHARMACEUTICALS, INC., 10350 NORTH TORREY PINES ROAD, LA JOLLA, CA, 92037
NUMBER OF CLAIMS:	41
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	84 Drawing Page(s)
LINE COUNT:	2350

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

```
=> d his

     (FILE 'HOME' ENTERED AT 16:59:27 ON 19 APR 2004)

     FILE 'MEDLINE, USPATFULL, DGENE, WPIDS, BIOSIS, FSTA, BIOBUSINESS'
     ENTERED AT 17:03:29 ON 19 APR 2004
L1         93950 S ATM OR ATAXIA TELANGIECTASIS
L2        114238 S P53
L3          6648 S ATR
L4           302 S L2 AND L3
L5            90 S L4 AND INHIBIT
L6             0 S L4 AND INHIBIT INTERACTION
L7            64 S L5 AND COMPOUND
L8            59 S L7 AND PEPTIDE

=> s l3 and l2
L9           302 L3 AND L2
```

```
=> s l1 and l2
L10       1284 L1 AND L2

=> s l10 and inhibit
L11        297 L10 AND INHIBIT

=> s l11 and inhibit interaction
L12          1 L11 AND INHIBIT INTERACTION

=> d l12 ti abs ibib tot

L12  ANSWER 1 OF 1  USPATFULL on STN
TI     System for detecting reporter gene expression
AB     An in vivo assay system for identifying chemical compounds that
       inhibit or promote a biological event is described. Test
       compounds may be assayed for their ability to induce the expression of a
       reporter gene which subsequently leads to the production of a reporter
       gene product. Preferably the reporter gene product is secreted from the
       cell or is membrane permeable so that the product is readily detectable.
       The signal from the reporter gene is preferably amplifiable so that even
       minute changes in expression of the reporter gene are detectable. The
       present invention also provided combinatorial libraries for use in the
       inventive assay system.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER:       2002:343927  USPATFULL
TITLE:                  System for detecting reporter gene expression
INVENTOR(S):            Shair, Matthew, Boston, MA, UNITED STATES
                        Chan, Lawrence, Cambridge, MA, UNITED STATES

                             NUMBER       KIND    DATE
                        ---------------- ------ --------
PATENT INFORMATION:     US 2002197653      A1   20021226
APPLICATION INFO.:      US 2002-91240      A1   20020305  (10)

                               NUMBER        DATE
                        ------------------ --------
PRIORITY INFORMATION:   US 2001-273736P    20010305 (60)
DOCUMENT TYPE:          Utility
FILE SEGMENT:           APPLICATION
LEGAL REPRESENTATIVE:   Choate, Hall & Stewart, Exchange Place, 53 State
                        Street, Boston, MA, 02109
NUMBER OF CLAIMS:       47
EXEMPLARY CLAIM:        1
NUMBER OF DRAWINGS:     11 Drawing Page(s)
LINE COUNT:             1315
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


=> d his

     (FILE 'HOME' ENTERED AT 16:59:27 ON 19 APR 2004)

     FILE 'MEDLINE, USPATFULL, DGENE, WPIDS, BIOSIS, FSTA, BIOBUSINESS'
     ENTERED AT 17:03:29 ON 19 APR 2004
L1         93950 S ATM OR ATAXIA TELANGIECTASIS
L2        114238 S P53
L3          6648 S ATR
L4           302 S L2 AND L3
L5            90 S L4 AND INHIBIT
L6             0 S L4 AND INHIBIT INTERACTION
L7            64 S L5 AND COMPOUND
L8            59 S L7 AND PEPTIDE
```

kinases in this checkpoint. We show that caffeine's ability to **inhibit** ATR (but not **ATM**) causes PCC, that ATR (but not **ATM**) prevents PCC, and that ATR prevents PCC via Chk-1 regulation. Moreover, mimicking cancer cell phenotypes by disrupting normal G(1) checkpoints sensitizes cells to PCC by ATR inhibition plus low-dose DNA damage. Notably, loss of **p53** function potently sensitizes cells to PCC caused by ATR inhibition by a small molecule. We present a molecular model for how ATR prevents PCC and suggest that ATR represents an attractive therapeutic target for selectively killing cancer cells by premature chromatin condensation.

ACCESSION NUMBER: 2001445854 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11481475
TITLE: ATR inhibition selectively sensitizes G1 checkpoint-deficient cells to lethal premature chromatin condensation.
AUTHOR: Nghiem P; Park P K; Kim Y; Vaziri C; Schreiber S L
CORPORATE SOURCE: Department of Chemistry and Chemical Biology, Howard Hughes Medical Institute, Harvard University, Cambridge, MA 02138, USA.
CONTRACT NUMBER: GM-52067 (NIGMS)
K08-AR0208703 (NIAMS)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2001 Jul 31) 98 (16) 9092-7. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010903
Entered Medline: 20010830

L11 ANSWER 10 OF 297 MEDLINE on STN
TI Regulation of the G2/M transition by **p53**.
AB **p53** protects mammals from neoplasia by inducing apoptosis, DNA repair and cell cycle arrest in response to a variety of stresses. **p53**-dependent arrest of cells in the G1 phase of the cell cycle is an important component of the cellular response to stress. Here we review recent evidence that implicates **p53** in controlling entry into mitosis when cells enter G2 with damaged DNA or when they are arrested in S phase due to depletion of the substrates required for DNA synthesis. Part of the mechanism by which **p53** blocks cells at the G2 checkpoint involves inhibition of Cdc2, the cyclin-dependent kinase required to enter mitosis. Cdc2 is inhibited simultaneously by three transcriptional targets of **p53**, Gadd45, p21, and 14-3-3 sigma. Binding of Cdc2 to Cyclin B1 is required for its activity, and repression of the cyclin B1 gene by **p53** also contributes to blocking entry into mitosis. **p53** also represses the cdc2 gene, to help ensure that cells do not escape the initial block. Genotoxic stress also activates **p53**-independent pathways that **inhibit** Cdc2 activity, activation of the protein kinases Chk1 and Chk2 by the protein kinases **Atm** and Atr. Chk1 and Chk2 **inhibit** Cdc2 by inactivating Cdc25, the phosphatase that normally activates Cdc2. Chk1, Chk2, **Atm** and Atr also contribute to the activation of **p53** in response to genotoxic stress and therefore play multiple roles. **p53** induces transcription of the reprimo, B99, and mcg10 genes, all of which contribute to the arrest of cells in G2, but the mechanisms of cell cycle arrest by these genes is not known. Repression of the topoisomerase II gene by **p53** helps to block entry into mitosis and strengthens the G2 arrest. In summary, multiple overlapping **p53**-dependent and **p53**-independent pathways regulate the G2/M transition in response to genotoxic stress.

ACCESSION NUMBER: 2001237339 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11313928
TITLE: Regulation of the G2/M transition by **p53**.
AUTHOR: Taylor W R; Stark G R
CORPORATE SOURCE: Department of Molecular Biology, Lerner Research Insititute, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA.
CONTRACT NUMBER: GM49345 (NIGMS)
SOURCE: Oncogene, (2001 Apr 5) 20 (15) 1803-15. Ref: 126
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010503

=> d his

(FILE 'HOME' ENTERED AT 16:59:27 ON 19 APR 2004)

FILE 'MEDLINE, USPATFULL, DGENE, WPIDS, BIOSIS, FSTA, BIOBUSINESS'
ENTERED AT 17:03:29 ON 19 APR 2004
L1 93950 S ATM OR ATAXIA TELANGIECTASIS
L2 114238 S P53
L3 6648 S ATR
L4 302 S L2 AND L3
L5 90 S L4 AND INHIBIT
L6 0 S L4 AND INHIBIT INTERACTION
L7 64 S L5 AND COMPOUND
L8 59 S L7 AND PEPTIDE
L9 302 S L3 AND L2
L10 1284 S L1 AND L2
L11 297 S L10 AND INHIBIT
L12 1 S L11 AND INHIBIT INTERACTION

=> s l11 and compound
L13 237 L11 AND COMPOUND

=> s l13 and peptide
L14 199 L13 AND PEPTIDE

=> d l14 ti abs ibib 1-15

L14 ANSWER 1 OF 199 USPATFULL on STN
TI Methods of diagnosis of colorectal cancer, compositions and methods of screening for modulators of colorectal cancer
AB Described herein are methods and compositions that can be used for diagnosis and treatment of colorectal cancer. Also described herein are methods that can be used to identify modulators of colorectal cancer.

ACCESSION NUMBER: 2004:82658 USPATFULL
TITLE: Methods of diagnosis of colorectal cancer, compositions and methods of screening for modulators of colorectal cancer
INVENTOR(S): Mack, David H., Menlo Park, CA, UNITED STATES
Markowitz, Sanford David, Pepper Pike, OH, UNITED STATES
Ried, Thomas, Bethesda, MD, UNITED STATES
PATENT ASSIGNEE(S): EOS Biotechnology, Inc. (U.S. corporation)

Case Western Reserve University (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004063108	A1	20040401
APPLICATION INFO.:	US 2002-318578	A1	20021212 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-340124P	20011213 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Albert P. Halluin, HOWREY SIMON ARNOLD & WHITE, LLP, 301 Ravenswood Avenue, Box 34, Menlo Park, CA, 94025
NUMBER OF CLAIMS: 51
EXEMPLARY CLAIM: 1
LINE COUNT: 3940

L14 ANSWER 2 OF 199 USPATFULL on STN

TI Treatment of kidney disease or renal failure using interleukin-1beta-converting enzyme (ICE)/CED-3 family inhibitors

AB The present invention provides methods and compositions for treating infectious disease or suppressing inflammation associated therewith or ameliorating symptoms thereof by the suppression of the activity of a member of the interleukin-1β-converting enzyme (ICE)/CED-3 family of proteases. Also provided are compositions useful for these purposes. Exemplary compounds useful in the methods of the invention are provided herein.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2004:77071 USPATFULL
TITLE: Treatment of kidney disease or renal failure using interleukin-1beta-converting enzyme (ICE)/CED-3 family inhibitors
INVENTOR(S): Fritz, Lawrence C., Rancho Santa Fe, CA, UNITED STATES
Tomaselli, Kevin J., San Diego, CA, UNITED STATES
Karanewsky, Donald S., Escondido, CA, UNITED STATES
Linton, Steven D., San Diego, CA, UNITED STATES
Bai, Xu, Carlsbad, CA, UNITED STATES
PATENT ASSIGNEE(S): Idun Pharmaceuticals, Inc., San Diego, CA, 92121 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004058850	A1	20040325
APPLICATION INFO.:	US 2003-653607	A1	20030902 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2002-208729, filed on 29 Jul 2002, PENDING Continuation of Ser. No. US 2001-7632, filed on 13 Nov 2001, GRANTED, Pat. No. US 6610683 Continuation-in-part of Ser. No. US 2001-982123, filed on 16 Oct 2001, GRANTED, Pat. No. US 6531467 Continuation-in-part of Ser. No. US 2000-737169, filed on 11 Dec 2000, ABANDONED Continuation of Ser. No. US 1997-979909, filed on 12 Sep 1997, GRANTED, Pat. No. US 6200969

	NUMBER	DATE
PRIORITY INFORMATION:	US 1996-26011P	19960912 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092
NUMBER OF CLAIMS: 15

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Page(s)
LINE COUNT: 4806
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 3 OF 199 USPATFULL on STN
TI Compounds and methods for therapy and diagnosis of lung cancer
AB Compounds and methods for the treatment and diagnosis of lung cancer are provided. The inventive compounds include polypeptides containing at least a portion of a lung tumor protein. Vaccines and pharmaceutical compositions for immunotherapy of lung cancer comprising such polypeptides, or DNA molecules encoding such polypeptides, are also provided, together with DNA molecules for preparing the inventive polypeptides.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2004:65812 USPATFULL
TITLE: Compounds and methods for therapy and diagnosis of lung cancer
INVENTOR(S): Wang, Tongtong, Medina, WA, United States
Hosken, Nancy A., Seattle, WA, United States
Kalos, Michael D., Seattle, WA, United States
Fanger, Gary R., Mill Creek, WA, United States
PATENT ASSIGNEE(S): Corixa Corporation, Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6706262	B1	20040316
APPLICATION INFO.:	US 1999-476496		19991230 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-466396, filed on 17 Dec 1999 Continuation-in-part of Ser. No. US 1999-285479, filed on 2 Apr 1999 Continuation-in-part of Ser. No. WO 1999-US5798, filed on 17 Mar 1999 Continuation-in-part of Ser. No. US 1998-221107, filed on 22 Dec 1998 Continuation-in-part of Ser. No. US 1998-123912, filed on 27 Jul 1998, now patented, Pat. No. US 6312695 Continuation-in-part of Ser. No. US 1998-40802, filed on 18 Mar 1998, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Chen, Shin-Lin
LEGAL REPRESENTATIVE: Seed IP Law Group PLLC
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 7543
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 4 OF 199 USPATFULL on STN
TI 14171 Protein kinase, a novel human protein kinase and uses thereof
AB The invention relates to a novel kinase nucleic acid sequence and protein. Also provided are vectors, host cells, and recombinant methods for making and using the novel molecules.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2004:63787 USPATFULL
TITLE: 14171 Protein kinase, a novel human protein kinase and uses thereof
INVENTOR(S): Kapeller-Libermann, Rosana, Chestnut Hill, MA, UNITED STATES
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc. (U.S. corporation)

	NUMBER	KIND	DATE

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004048305	A1	20040311
APPLICATION INFO.:	US 2003-658904	A1	20030910 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-781882, filed on 12 Feb 2001, GRANTED, Pat. No. US 6630335

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-182096P	20000211 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MILLENNIUM PHARMACEUTICALS, INC., 40 Landsdowne Street, CAMBRIDGE, MA, 02139
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 5414
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 5 OF 199 USPATFULL on STN
TI WT1 antisense oligos for the inhibition of breast cancer
AB The present invention provides methods for inhibiting the growth of breast cancer cells and methods for treating breast cancers expressing Wilms' Tumor 1 (WT1) gene product using a WT1 antisense oligonucleotide. It further provides methods of predicting breast cancer progression and methods for the screening of candidate substances for activity against breast cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2004:57943 USPATFULL
TITLE: WT1 antisense oligos for the inhibition of breast cancer
INVENTOR(S): Lopez-Berestein, Gabriel, Bellaire, TX, UNITED STATES
Tari, Ana Maria, Houston, TX, UNITED STATES
Zapata-Benavides, Pablo, Guadalupe NL, MEXICO
PATENT ASSIGNEE(S): Board of Regents, The University of Texas System (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004043950	A1	20040304
APPLICATION INFO.:	US 2003-336253	A1	20030103 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-345102P	20020103 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Priya D. Subramony, Fulbright & Jaworski L.L.P., Suite 2400, 600 Congress Avenue, Austin, TX, 78701
NUMBER OF CLAIMS: 53
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Page(s)
LINE COUNT: 3791
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 6 OF 199 USPATFULL on STN
TI Potentiation of cancer therapies by ZNF217 inhibition
AB This invention provides methods, reagents and kits for treating cancer in a patient or subject, e.g., a human. Accordingly, the present methods can be used to monitor the efficacy of a cancer treatment and to treat cancer, e.g., by inhibiting the expression and/or activity of ZNF217 in a neoplastic cell.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2004:50892 USPATFULL
TITLE:	Potentiation of cancer therapies by ZNF217 inhibition
INVENTOR(S):	Collins, Colin, San Rafael, CA, UNITED STATES Huang, Guiqing, San Bruno, CA, UNITED STATES Gray, Joe W., San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S):	REGENTS OF THE UNIVERSITY OF CALIFORNIA, Oakland, CA (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004038322	A1	20040226	
APPLICATION INFO.:	US 2003-349627	A1	20030122	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-351530P	20020122 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834
NUMBER OF CLAIMS:	32
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	12 Drawing Page(s)
LINE COUNT:	4283

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 7 OF 199 USPATFULL on STN

TI Methods of diagnosis of angiogenesis, compositions and methods of screening for angiogenesis modulators

AB Described herein are methods and compositions that can be used for diagnosis and treatment of angiogenic phenotypes and angiogenesis-associated diseases. Also described herein are methods that can be used to identify modulators of angiogenesis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2004:44503 USPATFULL
TITLE:	Methods of diagnosis of angiogenesis, compositions and methods of screening for angiogenesis modulators
INVENTOR(S):	Murray, Richard, Cupertino, CA, UNITED STATES Glynne, Richard, Palo Alto, CA, UNITED STATES Watson, Susan R., El Cerrito, CA, UNITED STATES Aziz, Natasha, Palo Alto, CA, UNITED STATES
PATENT ASSIGNEE(S):	Eos Biotechnology, Inc., South San Francisco, CA, UNITED STATES, 94080 (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004033495	A1	20040219	
APPLICATION INFO.:	US 2002-211462	A1	20020801	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-310025P	20010803 (60)
	US 2001-334244P	20011129 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834
NUMBER OF CLAIMS:	27
EXEMPLARY CLAIM:	1
LINE COUNT:	24599

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 8 OF 199 USPATFULL on STN
TI Drug screening systems and assays
AB A method of stimulating non-homologous end-joining (NHEJ) of DNA the method comprising performing NHEJ of DNA in the presence of inositol hexakisphosphate (IP.sub.6) or other stimulatory inositol phosphate. An assay of a protein kinase wherein the assay comprises inositol hexakisphosphate (IP.sub.6) or other stimulatory inositol phosphate. The invention also provides screening assays for compounds which may modulate NHEJ and which may be therapeutically useful; and screening assays for compounds which may modulate DNA-PK and related protein kinases and which may be therapeutically useful. Methods of modulating NHEJ and protein kinases are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2004:38591 USPATFULL			
TITLE:	Drug screening systems and assays			
INVENTOR(S):	West, Steve Craig, South Mimms Hertfordshire, UNITED KINGDOM Bartlett-Jones, Michael, London, UNITED KINGDOM Akemi Hanakahi, Leslyn Ann, Baltimore, MD, UNITED STATES			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004029130	A1	20040212	
APPLICATION INFO.:	US 2003-296014	A1	20030612	(10)
	WO 2001-GB2180		20010518	
	NUMBER		DATE	
PRIORITY INFORMATION:	GB 2000-12179		20000520	
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
LEGAL REPRESENTATIVE:	FISH & RICHARDSON PC, 225 FRANKLIN ST, BOSTON, MA, 02110			
NUMBER OF CLAIMS:	56			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	18 Drawing Page(s)			
LINE COUNT:	2260			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 9 OF 199 USPATFULL on STN
TI Methods of diagnosis of breast cancer, compositions and methods of screening for modulators of breast cancer
AB Described herein are genes whose expression are up-regulated or down-regulated in breast cancer. Related methods and compositions that can be used for diagnosis and treatment of breast cancer are disclosed. Also described herein are methods that can be used to identify modulators of breast cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2004:38576 USPATFULL			
TITLE:	Methods of diagnosis of breast cancer, compositions and methods of screening for modulators of breast cancer			
INVENTOR(S):	Mack, David H., Menlo Park, CA, UNITED STATES Gish, Kurt C., San Francisco, CA, UNITED STATES Afar, Daniel, Brisbane, CA, UNITED STATES			
PATENT ASSIGNEE(S):	Eos Technology, Inc., South San Francisco, CA, UNITED STATES, 94080-7019 (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004029114	A1	20040212	
APPLICATION INFO.:	US 2002-58270	A1	20020124	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-263965P	20010124 (60)
	US 2001-265928P	20010202 (60)
	US 2001-282698P	20010409 (60)
	US 2001-288590P	20010504 (60)
	US 2001-294443P	20010529 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1
LINE COUNT: 42494
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 10 OF 199 USPATFULL on STN
TI EphA2 monoclonal antibodies and methods of use thereof
AB The present invention relates to methods and compositions designed for the treatment, management, or prevention of cancer, particularly, metastatic cancer. In one embodiment, the methods of the invention comprise the administration of an effective amount of an antibody that binds to EphA2 and agonizes EphA2, thereby increasing EphA2 phosphorylation and decreasing EphA2 levels. In other embodiments, the methods of the invention comprise the administration of an effective amount of an antibody that binds to EphA2 and inhibits cancer cell colony formation in soft agar, inhibits tubular network formation in three-dimensional basement membrane or extracellular matrix preparation, preferentially binds to an EphA2 epitope that is exposed on cancer cells but not non-cancer cells, and/or has a low K.sub.off, thereby, inhibiting tumor cell growth and/or metastasis. The invention also provides pharmaceutical compositions comprising one or more EphA2 antibodies of the invention either alone or in combination with one or more other agents useful for cancer therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2004:38149 USPATFULL
TITLE: EphA2 monoclonal antibodies and methods of use thereof
INVENTOR(S): Kinch, Michael S., Laytonsville, MD, UNITED STATES
Carles-Kinch, Kelly, Laytonsville, MD, UNITED STATES
Kiener, Peter, Potomac, MD, UNITED STATES
Langermann, Solomon, Baltimore, MD, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004028685	A1	20040212	
APPLICATION INFO.:	US 2003-436782	A1	20030512	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-379322P	20020510 (60)
	US 2002-418213P	20021014 (60)
	US 2003-460507P	20030403 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PENNIE AND EDMONDS, 1155 AVENUE OF THE AMERICAS, NEW YORK, NY, 100362711
NUMBER OF CLAIMS: 95
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 27 Drawing Page(s)
LINE COUNT: 5596
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 11 OF 199 USPATFULL on STN
TI Antisense modulation of phosphotyrosyl phosphatase activator expression
AB Antisense compounds, compositions and methods are provided for modulating the expression of phosphotyrosyl phosphatase activator. The compositions comprise antisense compounds, particularly antisense oligonucleotides, targeted to nucleic acids encoding phosphotyrosyl phosphatase activator. Methods of using these compounds for modulation of phosphotyrosyl phosphatase activator expression and for treatment of diseases associated with expression of phosphotyrosyl phosphatase activator are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2004:31764 USPATFULL			
TITLE:	Antisense modulation of phosphotyrosyl phosphatase activator expression			
INVENTOR(S):	Dean, Nicholas M., Olivenhain, CA, UNITED STATES Dobie, Kenneth W., Del Mar, CA, UNITED STATES			
PATENT ASSIGNEE(S):	Isis Pharmaceuticals Inc. (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004023906	A1	20040205	
APPLICATION INFO.:	US 2002-211179	A1	20020801	(10)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
LEGAL REPRESENTATIVE:	WOODCOCK WASHBURN LLP, ONE LIBERTY PLACE - 46TH FLOOR, PHILADELPHIA, PA, 19103			
NUMBER OF CLAIMS:	20			
EXEMPLARY CLAIM:	1			
LINE COUNT:	7492			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 12 OF 199 USPATFULL on STN
TI Methods for detecting dna damage and screening for cancer therapeutics
AB A method for detecting DNA damage in a tissue sample involves contacting an immobilized biological sample with a labeled ligand which binds to human 53Bp1, and examining the immobilized sample for the presence of a label generated-detectable signal concentrated in foci in said sample. The presence of concentrated foci is indicative of DNA damage and the presence of diffuse signal is indicative of a normal sample. Diagnostic reagents contain a ligand that binds to human 53Bp1 associated with a detectable label. Diagnostic kits for detecting DNA damage in a biological sample contain such diagnostic reagents and signal detection components. Compositions that **inhibit** or antagonize the biological activity of 53Bp1 are identified by suitable assays, and are employed in methods of retarding the growth of a cancer cell.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2004:31097 USPATFULL			
TITLE:	Methods for detecting dna damage and screening for cancer therapeutics			
INVENTOR(S):	Halazonetis, Thanos, Wynnewood, PA, UNITED STATES Schultz, Linda B., Suwanee, GA, UNITED STATES			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004023235	A1	20040205	
APPLICATION INFO.:	US 2003-276312	A1	20030117	(10)
	WO 2001-US17471		20010530	
	NUMBER		DATE	
PRIORITY INFORMATION:	US 2000-60208716		20000601	
DOCUMENT TYPE:	Utility			

FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HOWSON AND HOWSON, ONE SPRING HOUSE CORPORATION CENTER, BOX 457, 321 NORRISTOWN ROAD, SPRING HOUSE, PA, 19477
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 2295
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 13 OF 199 USPATFULL on STN
TI Chromosome 3p21.3 genes are tumor suppressors
AB Tumor suppressor genes play a major role in the pathogenesis of human lung cancer and other cancers. Cytogenetic and allelotyping studies of fresh tumor and tumor-derived cell lines showed that cytogenetic changes and allele loss on the short arm of chromosome 3 (3p) are most frequently involved in about 90% of small cell lung cancers and greater than 50% of non-small cell lung cancers. A group of recessive oncogenes, Fus1, 101F6, Gene 21 (NPRL2), Gene 26 (CACNA2D2), Luca 1 (HYAL1), Luca 2 (HYAL2), PL6, 123F2 (RaSSFI), SEM A3 and Beta* (BLU), as defined by homozygous deletions in lung cancers, have been located and isolated at 3p21.3.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2004:20698 USPATFULL
TITLE: Chromosome 3p21.3 genes are tumor suppressors
INVENTOR(S): Ji, Lin, Sugar Land, TX, UNITED STATES
Minna, John Dorrance, Dallas, TX, UNITED STATES
Roth, Jack, Houston, TX, UNITED STATES
Lerman, Michael, Rockville, MD, UNITED STATES
PATENT ASSIGNEE(S): U.S. of America, represented by the Secretary, Department of Health and Human Services. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004016006	A1	20040122
APPLICATION INFO.:	US 2003-445718	A1	20030527 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-902003, filed on 10 Jul 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-217112P	20000710 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Steven L. Highlander, Esq., FULBRIGHT & JAWORSKI L.L.P., Suite 2400, 600 Congress Avenue, Austin, TX, 78701
NUMBER OF CLAIMS: 116
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 46 Drawing Page(s)
LINE COUNT: 5598
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 14 OF 199 USPATFULL on STN
TI Inhibiting retrotransposon and retroviral integration by targeting the **atm** pathway
AB Ataxia telangiectasia mutated (**ATM**)-dependent DNA damage signalling mechanisms are involved in retroviral and retrotransposon integration. Screening methods for inhibitors of retroviral and retrotranspons activity comprise inhibiting the **ATM**-dependent DNA damage signalling pathway, e.g. by disrupting interaction between components of the pathway. Inhibitors are useful as anti-retroviral agents, e.g. in inhibition of HIV.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2004:19397 USPATFULL
TITLE: Inhibiting retrotransposon and retroviral integration by targeting the **atm** pathway
INVENTOR(S): O'Connor, Mark James, Cambridge, UNITED KINGDOM
Jackson, Stephen Philip, Coton, Cambridge, UNITED KINGDOM
Lau, Alan, Cambridge, UNITED KINGDOM

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004014701	A1	20040122
APPLICATION INFO.:	US 2003-296845	A1	20030718 (10)
	WO 2001-GB2398		20010530

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BOZICEVIC, FIELD & FRANCIS LLP, 200 MIDDLEFIELD RD, SUITE 200, MENLO PARK, CA, 94025
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 1409
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 15 OF 199 USPATFULL on STN
TI Detection of heteroduplex polynucleotides using mutant nucleic acid repair enzymes with attenuated catalytic activity
AB Methods for detecting, localizing and removing abnormal base-pairing in a nucleic acid duplex are provided. These methods can be used for prognosis and diagnosis of diseases, disorders, pathogenic infections and nucleic acid polymorphisms. Combinations, kits and articles of manufacture for use in these methods are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2004:18781 USPATFULL
TITLE: Detection of heteroduplex polynucleotides using mutant nucleic acid repair enzymes with attenuated catalytic activity
INVENTOR(S): Yuan, Chong-Sheng, San Diego, CA, UNITED STATES
Datta, Abhijit, Carlsbad, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004014083	A1	20040122
APPLICATION INFO.:	US 2003-373238	A1	20030224 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-514016, filed on 25 Feb 2000, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Peng Chen, Morrison & Foerster LLP, Suite 500, 3811 Valley Centre Drive, San Diego, CA, 92130-2332
NUMBER OF CLAIMS: 105
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 10442
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> s assay method
L15 17472 ASSAY METHOD

=> s ATM () p53 () inhibit
L16 0 ATM (W) P53 (W) INHIBIT

```
=> s ATR () p53 () inhibit
L17          0 ATR (W) P53 (W) INHIBIT

=> s ATM () p53 () interaction
L18          0 ATM (W) P53 (W) INTERACTION

=> s inhibit ATM an p53
L19          0 INHIBIT ATM AN P53

=> s inhibit ATM and p53
L20         14 INHIBIT ATM AND P53

=> d l20 ti abs ibib tot

L20  ANSWER 1 OF 14      MEDLINE on STN
TI   ATM's leucine-rich domain and adjacent sequences are essential for ATM to
     regulate the DNA damage response.
AB   The ATM protein kinase regulates the DNA damage response by
     phosphorylating proteins involved in cell cycle checkpoints and DNA
     repair.  We report here on the function of the predicted leucine zipper
     (LZ) motif, and sequences adjacent to this, in regulating ATM activity.
     The predicted LZ sequence was deleted from ATM, generating ATMDeltaLZ, and
     expressed in an ATM-negative AT cell line.  ATM increased cell survival
     following exposure to ionizing radiation, whereas expression of ATMDeltaLZ
     failed to increase cell survival.  ATMDeltaLZ retained in vitro kinase
     activity, but was unable to phosphorylate p53 in vivo.  Leucine
     zippers mediate homo- and heterodimerization of proteins.  However, the
     predicted LZ of ATM did not mediate the formation of ATM dimers.  We
     examined if the predicted LZ of ATM was a dominant-negative inhibitor of
     ATM function in SW480 cells.  Expression of amino acids 769-1436 of ATM,
     including the predicted LZ, sensitized SW480 cells to ionizing radiation,
     but did not inhibit ATM's kinase activity or its
     ability to phosphorylate Brca1.  Further, this dominant-negative activity
     was not dependent on the predicted LZ domain.  The central region of the
     ATM protein therefore contains multiple sequences which regulate cell
     survival following DNA damage.
ACCESSION NUMBER:    2003447610      MEDLINE
DOCUMENT NUMBER:     PubMed ID: 14508513
TITLE:               ATM's leucine-rich domain and adjacent sequences are
                     essential for ATM to regulate the DNA damage response.
AUTHOR:              Chen Shujuan; Paul Proma; Price Brendan D
CORPORATE SOURCE:    Department of Radiation Oncology, JF513, Dana-Farber Cancer
                     Institute, Harvard Medical School, 44 Binney Street,
                     Boston, MA 02115, USA.
CONTRACT NUMBER:     CA64585 (NCI)
     CA93602 (NCI)
SOURCE:              Oncogene, (2003 Sep 25) 22 (41) 6332-9.
                     Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY:        England: United Kingdom
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200310
ENTRY DATE:          Entered STN: 20030926
                     Last Updated on STN: 20031024
                     Entered Medline: 20031023

L20  ANSWER 2 OF 14      MEDLINE on STN
TI   Protein kinase inhibitor 2-aminopurine overrides multiple genotoxic
     stress-induced cellular pathways to promote cell survival.
AB   2-Aminopurine (2-AP) is an adenine analog shown to cause cells to bypass
     chemical- and radiation-induced cell cycle arrest through as-yet
     unidentified mechanisms. 2-AP has also been shown to act as a kinase
```

inhibitor. Tumor suppressor **p53** plays an important role in the control of cell cycle and apoptosis in response to genotoxic stress. We were interested in examining the effect of 2-AP on **p53** phosphorylation and its possible consequences on checkpoint control in cells subjected to various forms of DNA damage. Here, we show that 2-AP suppresses **p53** phosphorylation in response to gamma radiation, adriamycin, or ultraviolet treatment. This is partly explained by the ability of the kinase inhibitor to **inhibit ATM** or ATR activities in vitro and impair ATM- or ATR-dependent **p53** phosphorylation in vivo. However, 2-AP is also capable of inhibiting **p53** phosphorylation in cells deficient in ATM, DNA-PK, or ATR suggesting the existence of multiple pathways by which this kinase inhibitor modulates **p53** activation. Biologically, the 2-AP-mediated inhibition of **p53** stabilization enables wild-type **p53**-containing cells to bypass adriamycin-induced G(2)/M arrest. In the long term, however, 2-AP facilitates cells to resist DNA damage-induced cell death independently of **p53**.

ACCESSION NUMBER: 2003275742 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12802279
TITLE: Protein kinase inhibitor 2-aminopurine overrides multiple genotoxic stress-induced cellular pathways to promote cell survival.
AUTHOR: Huang Shirley; Qu Li-Ke; Cuddihy Andrew R; Ragheb Rafik; Taya Yoichi; Koromilas Antonis E
CORPORATE SOURCE: Department of Microbiology and Immunology, McGill University, Montreal, Canada H3A 2T5.
SOURCE: Oncogene, (2003 Jun 12) 22 (24) 3721-33. Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030613
Last Updated on STN: 20030703
Entered Medline: 20030702

L20 ANSWER 3 OF 14 USPATFULL on STN
TI Inhibiting retrotransposon and retroviral integration by targeting the atm pathway
AB Ataxia telangiectasia mutated (ATM)-dependent DNA damage signalling mechanisms are involved in retroviral and retrotransposon integration. Screening methods for inhibitors of retroviral and retrotranspons activity comprise inhibiting the ATM-dependent DNA damage signalling pathway, e.g. by disrupting interaction between components of the pathway. Inhibitors are useful as anti-retroviral agents, e.g. in inhibition of HIV.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2004:19397 USPATFULL
TITLE: Inhibiting retrotransposon and retroviral integration by targeting the atm pathway
INVENTOR(S): O'Connor, Mark James, Cambridge, UNITED KINGDOM
Jackson, Stephen Philip, Coton, Cambridge, UNITED KINGDOM
Lau, Alan, Cambridge, UNITED KINGDOM

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004014701	A1	20040122	
APPLICATION INFO.:	US 2003-296845	A1	20030718	(10)
	WO 2001-GB2398		20010530	

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: BOZICEVIC, FIELD & FRANCIS LLP, 200 MIDDLEFIELD RD, SUITE 200, MENLO PARK, CA, 94025
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 1409
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 4 OF 14 USPATFULL on STN
TI ATM inhibitors
AB The application concerns a compound of formula I: ##STR1##

wherein one of P and Q is O, and the other of P and Q is CH, where there is a double bond between whichever of Q and P is CH and the carbon atom bearing the R.sup.3 group;

Y is either O or S;

R.sup.1 and R.sup.2 are independently hydrogen, an optionally substituted C.sub.1-7 alkyl group, C.sub.3-20 heterocyclyl group, or C.sub.5-20 aryl group, or may together form an optionally substituted heterocyclic ring having from 4 to 8 ring atoms;

R.sup.3 is a phenyl or pyridyl group, attached by a first bridge group selected from --S--, --S(.dbd.O)--, --S(.dbd.O).sub.2--, --O--, --NR.sup.N-- and CR.sup.C1R.sup.C2-- to an optionally substituted C.sub.5-20 carboaryl group, the phenyl or pyridyl group and optionally substituted C.sub.5-20 carboaryl group being optionally further linked by a second bridge group, so as to form an optionally substituted C.sub.5-7 ring, the phenyl or pyridyl group being further optionally substituted.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2004:2469 USPATFULL
TITLE: ATM inhibitors
INVENTOR(S): Murray Smith, Graeme Cameron, Cambridge, UNITED KINGDOM
Barr Martin, Niall Morrison, Cambridge, UNITED KINGDOM
Jackson, Stephen Philip, Cambridge, UNITED KINGDOM
O'Connor, Mark James, Cambridge, UNITED KINGDOM
Kai Lau, Alan Yin, Cambridge, UNITED KINGDOM
Cockcroft, Xiao-Ling Fan, Horsham, UNITED KINGDOM
Williams Matthews, Ian Timothy, Horsham, UNITED KINGDOM
Menear, Keith Allan, Horsham, UNITED KINGDOM
Martin Rigoreau, Laurent Jean, Horsham, UNITED KINGDOM
Hummersone, Marc Geoffery, Horsham, UNITED KINGDOM
Griffin, Roger John, Morpeth, UNITED KINGDOM
PATENT ASSIGNEE(S): Kudos Pharmaceuticals Ltd, Cambridge, UNITED KINGDOM (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004002492	A1	20040101	
APPLICATION INFO.:	US 2003-373114	A1	20030224	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	GB 2002-4350	20020225	
	US 2002-360493P	20020228	(60)
	US 2002-395884P	20020715	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MICHAEL BEST & FRIEDRICH, LLP, ONE SOUTH PINCKNEY STREET, P O BOX 1806, MADISON, WI, 53701
NUMBER OF CLAIMS: 13

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 3199
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 5 OF 14 USPATFULL on STN
TI ATM related kinase ATX, nucleic acids encoding same and methods of use
AB The invention provides an isolated nucleic acid molecule having substantially the same nucleotide sequence as SEQ ID NO:1. Also provided is an isolated oligonucleotide having at least 15 contiguous nucleotides of a nucleotide sequence referenced as SEQ ID NO:11. An isolated polypeptide having substantially the same amino acid sequence as SEQ ID NO:2 is further provided as well as an antibody, or antigen binding fragment thereof, which specifically binds to an ATX polypeptide and has an amino acid sequence as referenced in SEQ ID NO:2. A method for identifying an ATX-modulatory compound is additionally provided. The method consists of measuring the level of an ATX polypeptide in the presence of a test compound, wherein a difference in the level of said ATX polypeptide in the presence of said test compound compared to in the absence of said test compound indicating that said test compound is an ATX-modulatory compound, and wherein said ATX-modulatory compound is not caffeine or wortmannin.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:324700 USPATFULL
TITLE: ATM related kinase ATX, nucleic acids encoding same and methods of use
INVENTOR(S): Abraham, Robert T., San Diego, CA, UNITED STATES
Otterness, Diane M., San Diego, CA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003228675	A1	20031211	
APPLICATION INFO.:	US 2002-165216	A1	20020606	(10)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CAMPBELL & FLORES LLP, 4370 LA JOLLA VILLAGE DRIVE, 7TH FLOOR, SAN DIEGO, CA, 92122
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 18 Drawing Page(s)
LINE COUNT: 6825
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 6 OF 14 USPATFULL on STN
TI ATM kinase compositions and methods
AB The present invention provides methods for detecting activation of ATM kinase, DNA damage, and DNA damaging agents. Further provided are antibodies which specifically recognize the phosphorylation state of Ataxia Telangiectasia-Mutated (ATM) kinase. Methods of identifying agents which modulate the activation and activity of ATM kinase are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:225760 USPATFULL
TITLE: ATM kinase compositions and methods
INVENTOR(S): Kastan, Michael B., Cordova, TN, UNITED STATES
Bakkenist, Christopher, Cordova, TN, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003157572	A1	20030821	
APPLICATION INFO.:	US 2003-351733	A1	20030124	(10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2002-307077, filed

on 27 Nov 2002, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Licata & Tyrrell P.C., 66 E. Main Street, Marlton, NJ, 08053
NUMBER OF CLAIMS: 34
EXEMPLARY CLAIM: 1
LINE COUNT: 1587
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 7 OF 14 USPATFULL on STN
TI Expression and purification of ATM protein using vaccinia virus
AB The present disclosure concerns methods for recombinantly producing functional ataxia-telangiectasia (ATM) protein, methods for isolating recombinant functional ATM protein, and uses of ATM protein. In particular, a method is disclosed for using a vaccinia virus vector to express ATM, and using immunoprecipitation or affinity tagging to isolate recombinant ATM.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:187861 USPATFULL
TITLE: Expression and purification of ATM protein using vaccinia virus
INVENTOR(S): Gatti, Richard A., Sherman Oaks, CA, UNITED STATES
Chun, Helen H., Woodland Hills, CA, UNITED STATES
Rawlings, David J., Seattle, WA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003129651	A1	20030710	
APPLICATION INFO.:	US 2002-42775	A1	20020108	(10)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: KNOBBE MARTENS OLSON & BEAR LLP, 2040 MAIN STREET, FOURTEENTH FLOOR, IRVINE, CA, 92614
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 847
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 8 OF 14 USPATFULL on STN
TI ATM kinase compositions and methods
AB The present invention provides methods for detecting activation of ATM kinase, DNA damage, and DNA damaging agents. Further provided are antibodies which specifically recognize the phosphorylation state of Ataxia Telangiectasia-Mutated (ATM) kinase. Methods of identifying agents which modulate the activation and activity of ATM kinase are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:112929 USPATFULL
TITLE: ATM kinase compositions and methods
INVENTOR(S): Kastan, Michael B., Cordova, TN, UNITED STATES
Bakkenist, Christopher, Cordova, TN, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003077661	A1	20030424	
APPLICATION INFO.:	US 2002-307077	A1	20021127	(10)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Jane Massey Licata, Licata & Tyrrell P.C., 66 E. Main Street, Marlton, NJ, 08053

NUMBER OF CLAIMS: 28
EXEMPLARY CLAIM: 1
LINE COUNT: 1890
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 9 OF 14 USPATFULL on STN
TI ATM kinase modulation for screening and therapies
AB The present invention relates to identification of the consensus sequence phosphorylated by ATM kinase. This, in turn, permitted identification of ATM kinase target proteins, and development of a convenient assay system for ATM kinase phosphorylation using fusion polypeptides as substrates. The assay system is adaptable to screening for ATM modulators, particularly inhibitors. In a specific embodiment, the substrate recognition sequence and mutagenized variants of this sequence were incorporated in a GST fusion protein and assayed for phosphorylation by ATM kinase. This assay system is useful in screening for ATM inhibitors. ATM function assays were validated using an ATM-kinase dead dominant-negative mutant.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:30316 USPATFULL
TITLE: ATM kinase modulation for screening and therapies
INVENTOR(S): Kastan, Michael, Cordova, TN, UNITED STATES
Canman, Christine, Cordova, TN, UNITED STATES
Kim, Seong-Tae, Cordova, TN, UNITED STATES
Lim, Dae-Sik, Cordova, TN, UNITED STATES
PATENT ASSIGNEE(S): ST. JUDE CHILDREN'S RESEARCH HOSPITAL (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003022263	A1	20030130
APPLICATION INFO.:	US 2001-24123	A1	20011217 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 1999-400653, filed on 21 Sep 1999, PATENTED Continuation-in-part of Ser. No. US 1999-248061, filed on 10 Feb 1999, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: DARBY & DARBY P.C., 805 Third Avenue, New York, NY, 10022
NUMBER OF CLAIMS: 47
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 3517
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 10 OF 14 USPATFULL on STN
TI ATM kinase modulation for screening and therapies
AB The present invention relates to identification of the consensus sequence phosphorylated by ATM kinase. This, in turn, permitted identification of ATM kinase target proteins, and development of a convenient assay system for ATM kinase phosphorylation using fusion polypeptides as substrates. The assay system is adaptable to screening for ATM modulators, particularly inhibitors. In a specific embodiment, the substrate recognition sequence and mutagenized variants of this sequence were incorporated in a GST fusion protein and assayed for phosphorylation by ATM kinase. This assay system is useful in screening for ATM inhibitors. ATM function assays were validated using an ATM-kinase dead dominant-negative mutant.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:108831 USPATFULL
TITLE: ATM kinase modulation for screening and therapies
INVENTOR(S): Kastan, Michael, Cordova, TN, United States

	Canman, Christine, Cordova, TN, United States Kim, Seong-Tae, Cordova, TN, United States Lim, Dae-Sik, Cordova, TN, United States
PATENT ASSIGNEE(S):	St. Jude Children's Research Hospital, Memphis, TN, United States (U.S. corporation) Johns-Hopkins University, Baltimore, MD, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6387640	B1	20020514
APPLICATION INFO.:	US 1999-248061		19990210 (9)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Achutamurthy, Ponnathapu
ASSISTANT EXAMINER:	Monshipouri, M.
LEGAL REPRESENTATIVE:	Darby & Darby
NUMBER OF CLAIMS:	6
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT:	2258

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 11 OF 14 USPATFULL on STN

TI ATM kinase modulation for screening and therapies

AB The present invention relates to identification of the consensus sequence phosphorylated by ATM kinase. This, in turn, permitted identification of ATM kinase target proteins, and development of a convenient assay system for ATM kinase phosphorylation using fusion polypeptides as substrates. The assay system is adaptable to screening for ATM modulators, particularly inhibitors. In a specific embodiment, the substrate recognition sequence and mutagenized variants of this sequence were incorporated in a GST fusion protein and assayed for phosphorylation by ATM kinase. This assay system is useful in screening for ATM inhibitors. ATM function assays were validated using an ATM-kinase dead dominant-negative mutant.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:34294 USPATFULL
TITLE:	ATM kinase modulation for screening and therapies
INVENTOR(S):	Kastan, Michael, Cordova, TN, United States Canman, Christine, Cordova, TN, United States Kim, Seong-Tae, Cordova, TN, United States Lim, Dae-Sik, Cordova, TN, United States
PATENT ASSIGNEE(S):	St. Jude Childre's Research Hospital, Memphis, TN, United States (U.S. corporation) Johns-Hopkins University, Baltimore, MD, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6348311	B1	20020219
APPLICATION INFO.:	US 1999-400653		19990921 (9)

RELATED APPLN. INFO.:	Continuation of Ser. No. US 1999-248061, filed on 10 Feb 1999
DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Prouty, Rebecca E.
ASSISTANT EXAMINER:	Monshipouri, Maryam
LEGAL REPRESENTATIVE:	Darby & Darby
NUMBER OF CLAIMS:	2
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	9 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT:	3229

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 12 OF 14 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
TI Identifying the activated state of ataxia-telangiectasia mutated kinase, e.g. for detecting DNA damage, comprises determining the phosphorylation state of serine-1981.
AN 2003-766153 [72] WPIDS
CR 2003-567379 [53]
AB US2003157572 A UPAB: 20031107
NOVELTY - Identifying the activated state of ataxia-telangiectasia mutated kinase (M1) comprising determining the phosphorylation state of serine-1981, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) antibody that specifically recognizes the phosphorylation state of serine-1981 of ataxia-telangiectasia mutated (ATM) kinase;

(2) detecting DNA damage (M2) in a sample by identifying the activated state of ATM kinase as above;

(3) detecting a DNA-damaging agent (M3) in a sample by contacting an cell containing ATM kinase with the sample and identifying the activated state of the ATM kinase as above;

(4) kit for detecting a DNA-damaging agent, comprising an antibody as above;

(5) production of soluble ATM kinase (M4) or a fragment thereof by contacting a polypeptide containing the ATM kinase domain with a polypeptide containing serine-1981 of ATM kinase;

(6) identifying an agent (M5) that modulates the activated state of ATM kinase by contacting an cell containing ATM kinase with an agent and identifying the activated state of the ATM kinase as above;

(7) enhancing a cellular response to DNA damage by administering an agent (I) that agonizes the activation of ATM kinase;

(8) identifying an agent (M6) that inhibits ATM kinase activity by contacting soluble ATM kinase protein with the agent and a phosphate donor and determining the phosphorylation state of serine-1981.

USE - The method is useful for detecting DNA damage and DNA-damaging agents, identifying agents that modulate the activated state of ATM kinase and identifying agents that **inhibit ATM** kinase activity (claimed).

Dwg.0/0

ACCESSION NUMBER: 2003-766153 [72] WPIDS
CROSS REFERENCE: 2003-567379 [53]
DOC. NO. NON-CPI: N2003-613679
DOC. NO. CPI: C2003-210477
TITLE: Identifying the activated state of ataxia-telangiectasia mutated kinase, e.g. for detecting DNA damage, comprises determining the phosphorylation state of serine-1981.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): BAKKENIST, C; KASTAN, M B
PATENT ASSIGNEE(S): (BAKK-I) BAKKENIST C; (KAST-I) KASTAN M B
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2003157572	A1	20030821	(200372)*		16

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2003157572	A1 CIP of	US 2002-307077	20021127
		US 2003-351733	20030124

PRIORITY APPLN. INFO: US 2003-351733 20030124; US 2002-307077 20021127

L20 ANSWER 13 OF 14 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
TI ATM's leucine-rich domain and adjacent sequences are essential for ATM to regulate the DNA damage response.
AB The ATM protein kinase regulates the DNA damage response by phosphorylating proteins involved in cell cycle checkpoints and DNA repair. We report here on the function of the predicted leucine zipper (LZ) motif, and sequences adjacent to this, in regulating ATM activity. The predicted LZ sequence was deleted from ATM, generating ATMDELTALZ, and expressed in an ATM-negative AT cell line. ATM increased cell survival following exposure to ionizing radiation, whereas expression of ATMDELTALZ failed to increase cell survival. ATMDELTALZ retained in vitro kinase activity, but was unable to phosphorylate **p53** in vivo. Leucine zippers mediate homo- and heterodimerization of proteins. However, the predicted LZ of ATM did not mediate the formation of ATM dimers. We examined if the predicted LZ of ATM was a dominant-negative inhibitor of ATM function in SW480 cells. Expression of amino acids 769-1436 of ATM, including the predicted LZ, sensitized SW480 cells to ionizing radiation, but did not **inhibit ATM**'s kinase activity or its ability to phosphorylate Brca1. Further, this dominant-negative activity was not dependent on the predicted LZ domain. The central region of the ATM protein therefore contains multiple sequences which regulate cell survival following DNA damage.
ACCESSION NUMBER: 2003:494842 BIOSIS
DOCUMENT NUMBER: PREV200300485973
TITLE: ATM's leucine-rich domain and adjacent sequences are essential for ATM to regulate the DNA damage response.
AUTHOR(S): Chen, Shujuan; Paul, Proma; Price, Brendan D. [Reprint Author]
CORPORATE SOURCE: Department of Radiation Oncology, Dana-Farber Cancer Institute, Harvard Medical School, 44 Binney Street, JF513, Boston, MA, 02115, USA
brendan_price@dfci.harvard.edu
SOURCE: Oncogene, (25 September 2003) Vol. 22, No. 41, pp. 6332-6339. print.
ISSN: 0950-9232 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Oct 2003
Last Updated on STN: 22 Oct 2003

L20 ANSWER 14 OF 14 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
TI Protein kinase inhibitor 2-aminopurine overrides multiple genotoxic stress-induced cellular pathways to promote cell survival.
AB 2-Aminopurine (2-AP) is an adenine analog shown to cause cells to bypass chemical- and radiation-induced cell cycle arrest through as-yet unidentified mechanisms. 2-AP has also been shown to act as a kinase inhibitor. Tumor suppressor **p53** plays an important role in the control of cell cycle and apoptosis in response to genotoxic stress. We were interested in examining the effect of 2-AP on **p53** phosphorylation and its possible consequences on checkpoint control in cells subjected to various forms of DNA damage. Here, we show that 2-AP suppresses **p53** phosphorylation in response to gamma radiation, adriamycin, or ultraviolet treatment. This is partly explained by the ability of the kinase inhibitor to **inhibit ATM** or ATR activities in vitro and impair ATM- or ATR-dependent **p53** phosphorylation in vivo. However, 2-AP is also capable of inhibiting **p53** phosphorylation in cells deficient in ATM, DNA-PK, or ATR suggesting the existence of multiple pathways by which this kinase inhibitor modulates **p53** activation. Biologically, the 2-AP-mediated inhibition of **p53** stabilization enables wildtype **p53**-containing cells to bypass adriamycin-induced G2/M arrest. In

the long term, however, 2-AP facilitates cells to resist DNA damage-induced cell death independently of **p53**.

ACCESSION NUMBER: 2003:314356 BIOSIS
DOCUMENT NUMBER: PREV200300314356
TITLE: Protein kinase inhibitor 2-aminopurine overrides multiple genotoxic stress-induced cellular pathways to promote cell survival.
AUTHOR(S): Huang, Shirley; Qu, Li-Ke; Cuddihy, Andrew R.; Ragheb, Rafik; Taya, Yoichi; Koromilas, Antonis E. [Reprint Author]
CORPORATE SOURCE: Department of Microbiology and Immunology, McGill University, Montreal, H3A 2T5, Canada
antonis.koromilas@mcgill.ca
SOURCE: Oncogene, (12 June 2003) Vol. 22, No. 24, pp. 3721-3733. print.
ISSN: 0950-9232 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Jul 2003
Last Updated on STN: 9 Jul 2003

=> s ATM and inhibit
L21 5813 ATM AND INHIBIT

=> s ATR and inhibit
L22 575 ATR AND INHIBIT

=> s ATM inhibition
L23 9 ATM INHIBITION

=> s ATR inhibition
L24 3 ATR INHIBITION

=> d l23 ti abs ibib tot

L23 ANSWER 1 OF 9 USPATFULL on STN
TI ATM inhibitors
AB The application concerns a compound of formula I: ##STR1##

wherein one of P and Q is O, and the other of P and Q is CH, where there is a double bond between whichever of Q and P is CH and the carbon atom bearing the R.sup.3 group;

Y is either O or S;

R.sup.1 and R.sup.2 are independently hydrogen, an optionally substituted C.sub.1-7 alkyl group, C.sub.3-20 heterocyclyl group, or C.sub.5-20 aryl group, or may together form an optionally substituted heterocyclic ring having from 4 to 8 ring atoms;

R.sup.3 is a phenyl or pyridyl group, attached by a first bridge group selected from --S--, --S(.dbd.O)--, --S(.dbd.O).sub.2--, --O--, --NR.sup.N-- and CR.sup.C1R.sup.C2-- to an optionally substituted C.sub.5-20 carboaryl group, the phenyl or pyridyl group and optionally substituted C.sub.5-20 carboaryl group being optionally further linked by a second bridge group, so as to form an optionally substituted C.sub.5-7 ring, the phenyl or pyridyl group being further optionally substituted.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2004:2469 USPATFULL
TITLE: ATM inhibitors
INVENTOR(S): Murray Smith, Graeme Cameron, Cambridge, UNITED KINGDOM
Barr Martin, Niall Morrison, Cambridge, UNITED KINGDOM

Jackson, Stephen Philip, Cambridge, UNITED KINGDOM
O'Connor, Mark James, Cambridge, UNITED KINGDOM
Kai Lau, Alan Yin, Cambridge, UNITED KINGDOM
Cockcroft, Xiao-Ling Fan, Horsham, UNITED KINGDOM
Williams Matthews, Ian Timothy, Horsham, UNITED KINGDOM
Menear, Keith Allan, Horsham, UNITED KINGDOM
Martin Rigoreau, Laurent Jean, Horsham, UNITED KINGDOM
Hummersone, Marc Geoffery, Horsham, UNITED KINGDOM
Griffin, Roger John, Morpeth, UNITED KINGDOM

PATENT ASSIGNEE(S): Kudos Pharmaceuticals Ltd, Cambridge, UNITED KINGDOM (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004002492	A1	20040101
APPLICATION INFO.:	US 2003-373114	A1	20030224 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	GB 2002-4350	20020225
	US 2002-360493P	20020228 (60)
	US 2002-395884P	20020715 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MICHAEL BEST & FRIEDRICH, LLP, ONE SOUTH PINCKNEY STREET, P O BOX 1806, MADISON, WI, 53701
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 3199
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L23 ANSWER 2 OF 9 USPATFULL on STN
TI ATM kinase modulation for screening and therapies
AB The present invention relates to identification of the consensus sequence phosphorylated by ATM kinase. This, in turn, permitted identification of ATM kinase target proteins, and development of a convenient assay system for ATM kinase phosphorylation using fusion polypeptides as substrates. The assay system is adaptable to screening for ATM modulators, particularly inhibitors. In a specific embodiment, the substrate recognition sequence and mutagenized variants of this sequence were incorporated in a GST fusion protein and assayed for phosphorylation by ATM kinase. This assay system is useful in screening for ATM inhibitors. ATM function assays were validated using an ATM-kinase dead dominant-negative mutant.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:30316 USPATFULL
TITLE: ATM kinase modulation for screening and therapies
INVENTOR(S): Kastan, Michael, Cordova, TN, UNITED STATES
Canman, Christine, Cordova, TN, UNITED STATES
Kim, Seong-Tae, Cordova, TN, UNITED STATES
Lim, Dae-Sik, Cordova, TN, UNITED STATES
PATENT ASSIGNEE(S): ST. JUDE CHILDREN'S RESEARCH HOSPITAL (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003022263	A1	20030130
APPLICATION INFO.:	US 2001-24123	A1	20011217 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 1999-400653, filed on 21 Sep 1999, PATENTED Continuation-in-part of Ser. No. US 1999-248061, filed on 10 Feb 1999, PENDING
DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: DARBY & DARBY P.C., 805 Third Avenue, New York, NY, 10022
NUMBER OF CLAIMS: 47
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 3517
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L23 ANSWER 3 OF 9 USPATFULL on STN
TI ATM kinase modulation for screening and therapies
AB The present invention relates to identification of the consensus sequence phosphorylated by ATM kinase. This, in turn, permitted identification of ATM kinase target proteins, and development of a convenient assay system for ATM kinase phosphorylation using fusion polypeptides as substrates. The assay system is adaptable to screening for ATM modulators, particularly inhibitors. In a specific embodiment, the substrate recognition sequence and mutagenized variants of this sequence were incorporated in a GST fusion protein and assayed for phosphorylation by ATM kinase. This assay system is useful in screening for ATM inhibitors. ATM function assays were validated using an ATM-kinase dead dominant-negative mutant.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:108831 USPATFULL
TITLE: ATM kinase modulation for screening and therapies
INVENTOR(S): Kastan, Michael, Cordova, TN, United States
Canman, Christine, Cordova, TN, United States
Kim, Seong-Tae, Cordova, TN, United States
Lim, Dae-Sik, Cordova, TN, United States
PATENT ASSIGNEE(S): St. Jude Children's Research Hospital, Memphis, TN, United States (U.S. corporation)
Johns-Hopkins University, Baltimore, MD, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6387640	B1	20020514	
APPLICATION INFO.:	US 1999-248061		19990210	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Achutamurthy, Ponnathapu
ASSISTANT EXAMINER: Monshipouri, M.
LEGAL REPRESENTATIVE: Darby & Darby
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 2258
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L23 ANSWER 4 OF 9 USPATFULL on STN
TI ATM kinase modulation for screening and therapies
AB The present invention relates to identification of the consensus sequence phosphorylated by ATM kinase. This, in turn, permitted identification of ATM kinase target proteins, and development of a convenient assay system for ATM kinase phosphorylation using fusion polypeptides as substrates. The assay system is adaptable to screening for ATM modulators, particularly inhibitors. In a specific embodiment, the substrate recognition sequence and mutagenized variants of this sequence were incorporated in a GST fusion protein and assayed for phosphorylation by ATM kinase. This assay system is useful in screening for ATM inhibitors. ATM function assays were validated using an ATM-kinase dead dominant-negative mutant.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:34294 USPATFULL
TITLE:	ATM kinase modulation for screening and therapies
INVENTOR(S):	Kastan, Michael, Cordova, TN, United States Canman, Christine, Cordova, TN, United States Kim, Seong-Tae, Cordova, TN, United States Lim, Dae-Sik, Cordova, TN, United States
PATENT ASSIGNEE(S):	St. Jude Childre's Research Hospital, Memphis, TN, United States (U.S. corporation) Johns-Hopkins University, Baltimore, MD, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6348311	B1	20020219
APPLICATION INFO.:	US 1999-400653		19990921 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1999-248061, filed on 10 Feb 1999		

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Prouty, Rebecca E.
ASSISTANT EXAMINER:	Monshipouri, Maryam
LEGAL REPRESENTATIVE:	Darby & Darby
NUMBER OF CLAIMS:	2
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	9 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT:	3229

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L23 ANSWER 5 OF 9 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

TI New 2-amino-6-(hetero)aryl-thiopyran-4-one derivatives are DNA protein kinase inhibitors, useful for treating cancer.

AN 2003-278515 [27] WPIDS

AB WO2003015790 A UPAB: 20030429

NOVELTY - 2-Amino-6-(hetero)aryl-thiopyran-4-one derivatives (I) are new.

DETAILED DESCRIPTION - 2-Amino-6-(hetero)aryl-thiopyran-4-one derivatives of formula (I), and their isomers, salts, solvates and prodrugs, are new.

R1, R2 = H, optionally substituted 1-7C alkyl, 3-20C heterocyclyl or 5-20C aryl; or

NR1R2 = substituted heterocyclic having 4-8 ring atoms; and

R3 = optionally substituted 3-20C heterocyclyl or 5-20C aryl.

ACTIVITY - Cytostatic; Virucide.

MECHANISM OF ACTION - DNA Protein Kinase Inhibitors.

Tests were carried out to determine:

(a) DNA-PK inhibition;

(b) PI 3-kinase inhibition; and

(c) **ATM inhibition**.

The resulting IC50 values for 2 morpholin-4-yl-6-phenyl-thiopyran-4-one were (a) 0.6 micro M; (b) 10 micro M; and (c) greater than 100 micro M. Selectivity for DNA-PK/PI 3K was 17; and selectivity for DNA-PK/ATM was greater than 167.

USE - For inhibiting activity of DNA protein kinase; as an adjunct in cancer therapy or for potentiating tumor cells for treatment with ionizing radiation or chemotherapeutic agents; for treating a retroviral mediated disease or a disease ameliorated by the inhibition of DNA-PK, or cancer (claimed).

Dwg.0/0

ACCESSION NUMBER:	2003-278515 [27] WPIDS
DOC. NO. CPI:	C2003-072845
TITLE:	New 2-amino-6-(hetero)aryl-thiopyran-4-one derivatives are DNA protein kinase inhibitors, useful for treating cancer.
DERWENT CLASS:	B03

INVENTOR(S): CALVERT, H A; CURTIN, N J; GOLDING, B T; GRIFFIN, R J; HARDCASTLE, I R; MARTIN, N M B; NEWELL, D R; NUTLEY, B P; RAYNAUD, F I; RIGOREAU, L J M; SMITH, G C M; WORKMAN, P
PATENT ASSIGNEE(S): (CANC-N) CANCER RES TECHNOLOGY LTD
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003015790	A1	20030227	(200327)*	EN	70

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003015790	A1	WO 2002-GB3740	20020814

PRIORITY APPLN. INFO: GB 2001-19863 20010814

L23 ANSWER 6 OF 9 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
TI Mechanism of DNA damage-induced S phase arrest and abrogation by caffeine and UCN-01.
ACCESSION NUMBER: 2003:451987 BIOSIS
DOCUMENT NUMBER: PREV200300451987
TITLE: Mechanism of DNA damage-induced S phase arrest and abrogation by caffeine and UCN-01.
AUTHOR(S): Kohn, Ethan A. [Reprint Author]; East-man, Alan [Reprint Author]
CORPORATE SOURCE: Dartmouth Medical School, Hanover, NH, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 545. print.
Meeting Info.: 94th Annual Meeting of the American Association for Cancer Research. Washington, DC, USA. July 11-14, 2003.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Oct 2003
Last Updated on STN: 1 Oct 2003

L23 ANSWER 7 OF 9 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
TI CARBON DIOXIDE INHIBITION OF PHOTOSYNTHETIC GROWTH OF CHLORELLA.
AB Chlorella cultures were grown in a tubular loop reactor which facilitated both irradiation of the culture and gas mixing compared with a conventional stired vessel with vortex aeration. Measurements of the inhibition of maximum specific growth rate (proportional to photosynthetic rate) in the tubulr reactor showded tht CO2 behaves as a typical inhibitory subtstrate at partial pressures (PCO2) up to 0.6 atmospheric The PCO2 for 50% reduction in maximum specific growth rate was 0.36 atmospheric At 0.6 atm there was a discontinuity in the inhibitory effect with a sharp increase in the inhibitory effect at higher PCO2 values. Cultures rapidly adjusted to step changes in the PCO2 up to 0.6 atmospheric At a PCO2 of 1 **atm inhibition** was complete but the inhibitory effect was readily reversed.

ACCESSION NUMBER: 1985:291379 BIOSIS
DOCUMENT NUMBER: PREV198579071375; BA79:71375
TITLE: CARBON DIOXIDE INHIBITION OF PHOTOSYNTHETIC GROWTH OF CHLORELLA.
AUTHOR(S): SILVA H J [Reprint author]; PIRT S J
CORPORATE SOURCE: CAT MICROBIOL INDUSTRIAL, UNIV NACIONAL SAN LUIS, CHACABUCO Y PEDERNA, 5700 SAN LUIS, ARGENTINA
SOURCE: Journal of General Microbiology, (1984) Vol. 130, No. 11, pp. 2833-2838.
CODEN: JGMIAN. ISSN: 0022-1287.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH

L23 ANSWER 8 OF 9 FSTA COPYRIGHT 2004 IFIS on STN
TI Minimal methods of food preservation.
AN 1988(09):E0009 FSTA
AB The author discusses the concept of minimal methods of food preservation in terms of 4 basic processes: inactivation of microorganisms by heat (HTST, UHT, extrusion, microwave); selection (fermentation, membrane fractionation, modified **atm.**); **inhibition** (dehydration, low temperature, chemical inhibitors or preservatives) and prevention (good manufacturing practice, hygiene and packaging). The use of interdisciplinary research groups at Reading University to study the most effective combinations of these processes is underway. The author also considers the concept of minimal food preservation techniques and food technology as part of the much wider field of world food supplies and their present unequal distribution. He suggest ways in which western countries can learn from primitive methods of food fermentation (i.e. the original form of biotechnology) by encouraging more technologists from developing countries to bring their expertise to research projects at the University. The history of food technology dates back to the first record of the stone milling of cereals in 10 000 BC, with primitive methods of fermentation, salting, drying and smoking also dating back thousands of years. The need to continue this process of development to ensure the equal distribution of wholesome, safe and varied food supplies throughout the world is emphasized.
TITLE: Minimal methods of food preservation.
AUTHOR: Campbell-Platt, G.
CORPORATE SOURCE: Dep. of Food Tech., Univ. of Reading, Whiteknights Park, Reading, UK
SOURCE: Food Science & Technology Today, (1988) 2 (2) 95-98, 100-101, 103
ISSN: 0950-9623
DOCUMENT TYPE: Journal
LANGUAGE: English

L23 ANSWER 9 OF 9 FSTA COPYRIGHT 2004 IFIS on STN
TI Shelf-life studies on carbon dioxide packaged fin-fish from the Gulf of Mexico.
AN 1980(06):R0385 FSTA
AB Modified atm packaging using CO.sub.2 was demonstrated to be effective in retarding the growth of microorganisms during storage of fresh fish from the Gulf of Mexico. At 4° C, there was at least a log difference in bacterial counts at 2, 4, and 6 days between fish stored in CO.sub.2 as compared to control fish stored without CO.sub.2. While the CO.sub.2 atm was shown to inhibit the growth of common spoilage types of bacteria such as Gram-negative rods (Pseudomonas), stimulation of Gram-positive bacteria such as Lactobacillus was also demonstrated. Fish stored at 4° C for 2-8 days in a modified atm containing CO.sub.2 had lower total volatile N values than fish stored at the same temperature without CO.sub.2. The results indicate that an extension of the shelf-life of fresh fish can be obtained by packaging and storing the fish in a CO.sub.2 atmospheric

TITLE: Shelf-life studies on carbon dioxide packaged fin-fish from the Gulf of Mexico.
AUTHOR: Banks, H.; Nickelson, R., II; Finne, G.
CORPORATE SOURCE: Anim. Sci. Dep., Texas A&M Univ., College Station, Texas 77843, USA
SOURCE: Journal of Food Science, (1980) 45 (2) 157-162
DOCUMENT TYPE: Journal
LANGUAGE: English

=> d 124 ti abs ibib tot

L24 ANSWER 1 OF 3 MEDLINE on STN
TI **ATR inhibition** selectively sensitizes G1 checkpoint-deficient cells to lethal premature chromatin condensation.
AB Premature chromatin condensation (PCC) is a hallmark of mammalian cells that begin mitosis before completing DNA replication. This lethal event is prevented by a highly conserved checkpoint involving an unknown, caffeine-sensitive mediator. Here, we have examined the possible involvement of the caffeine-sensitive ATM and ATR protein kinases in this checkpoint. We show that caffeine's ability to inhibit ATR (but not ATM) causes PCC, that ATR (but not ATM) prevents PCC, and that ATR prevents PCC via Chk-1 regulation. Moreover, mimicking cancer cell phenotypes by disrupting normal G(1) checkpoints sensitizes cells to PCC by **ATR inhibition** plus low-dose DNA damage. Notably, loss of p53 function potently sensitizes cells to PCC caused by **ATR inhibition** by a small molecule. We present a molecular model for how ATR prevents PCC and suggest that ATR represents an attractive therapeutic target for selectively killing cancer cells by premature chromatin condensation.
ACCESSION NUMBER: 2001445854 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11481475
TITLE: **ATR inhibition** selectively sensitizes G1 checkpoint-deficient cells to lethal premature chromatin condensation.
AUTHOR: Nghiem P; Park P K; Kim Y; Vaziri C; Schreiber S L
CORPORATE SOURCE: Department of Chemistry and Chemical Biology, Howard Hughes Medical Institute, Harvard University, Cambridge, MA 02138, USA.
CONTRACT NUMBER: GM-52067 (NIGMS)
K08-AR0208703 (NIAMS)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2001 Jul 31) 98 (16) 9092-7. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010903
Entered Medline: 20010830

L24 ANSWER 2 OF 3 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
TI All-trans-retinal is a closed-state inhibitor of rod cyclic nucleotide-gated (CNG) channels.
AB CNG channels in the plasma membrane of retinal rods are closed upon photoactivation of rhodopsin and induction of a G-protein cascade. Millimolar levels of all-trans-retinal (ATR) are expected to be released from rhodopsin upon exposure to bright light. We have previously shown that ATR inhibits rod CNG channels with an IC50 in the nanomolar range at near physiological levels of cGMP in excised, inside-out Xenopus oocytes. Here we examine **ATR inhibition** of rod CNG channels in more detail. Our results and a quantitative model suggest that ATR

prefers closed, unliganded channels over open, fully liganded channels. However, it appears that ATR can bind fully liganded, open channels, but drives them into a non-conducting state. This is in contrast to olfactory channels, which appear able to open even when associated with ATR. We also provide evidence that **ATR inhibition** has no voltage dependence beyond the weak voltage dependence of channel gating. Inhibition by ATR was found to be more potent and much faster when ATR was applied to the intracellular, rather than extracellular side of the membrane. This is consistent with an ATR binding site accessible from the intracellular side of the channel or an interaction of ATR with the inner leaflet of the bilayer. Finally, some evidence suggests that inhibition of the channel by ATR may involve a Schiff base reaction: hydroxylamine (a Schiff base destabilizing agent) slowed **ATR inhibition** significantly; beta-ionone, which lacks the terminal ATR aldehyde group, did not inhibit the channel. These results imply that ATR is a voltage-independent, closed-state inhibitor of rod CNG channels that may play a role in photoreceptor responses after exposure to bright light.

ACCESSION NUMBER: 2004:124305 BIOSIS
DOCUMENT NUMBER: PREV200400127228
TITLE: All-trans-retinal is a closed-state inhibitor of rod cyclic nucleotide-gated (CNG) channels.
AUTHOR(S): Pelosi, Diana M. [Reprint Author]; Tetreault, Michelle L. [Reprint Author]; McCabe, Sarah L. [Reprint Author]; Zimmerman, Anita L. [Reprint Author]
CORPORATE SOURCE: Molecular Pharmacology, Physiology, and Biotechnology, Brown University, Providence, RI, USA
SOURCE: Biophysical Journal, (January 2004) Vol. 86, No. 1, pp. 292a-293a. print.
Meeting Info.: 48th Annual Meeting of the Biophysical Society. Baltimore, MD, USA. February 14-18, 2004. Biophysical Society.
ISSN: 0006-3495 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Mar 2004
Last Updated on STN: 3 Mar 2004

L24 ANSWER 3 OF 3 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
TI **ATR inhibition** selectively sensitizes G1 checkpoint-deficient cells to lethal premature chromatin condensation.
AB Premature chromatin condensation (PCC) is a hallmark of mammalian cells that begin mitosis before completing DNA replication. This lethal event is prevented by a highly conserved checkpoint involving an unknown, caffeine-sensitive mediator. Here, we have examined the possible involvement of the caffeine-sensitive ATM and ATR protein kinases in this checkpoint. We show that caffeine's ability to inhibit ATR (but not ATM) causes PCC, that ATR (but not ATM) prevents PCC, and that ATR prevents PCC via Chk-1 regulation. Moreover, mimicking cancer cell phenotypes by disrupting normal G1 checkpoints sensitizes cells to PCC by **ATR inhibition** plus low-dose DNA damage. Notably, loss of p53 function potently sensitizes cells to PCC caused by **ATR inhibition** by a small molecule. We present a molecular model for how ATR prevents PCC and suggest that ATR represents an attractive therapeutic target for selectively killing cancer cells by premature chromatin condensation.

ACCESSION NUMBER: 2001:421050 BIOSIS
DOCUMENT NUMBER: PREV200100421050
TITLE: **ATR inhibition** selectively sensitizes G1 checkpoint-deficient cells to lethal premature chromatin condensation.
AUTHOR(S): Nghiem, Paul; Park, Peter K.; Kim, Yong-son; Vaziri, Cyrus; Schreiber, Stuart L. [Reprint author]
CORPORATE SOURCE: Department of Chemistry and Chemical Biology, Howard Hughes

Medical Institute, Harvard University, Cambridge, MA, 02138, USA
sls@slsiris.harvard.edu

SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (July 31, 2001) Vol. 98, No. 16, pp. 9092-9097. print.
CODEN: PNASA6. ISSN: 0027-8424.

DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Sep 2001
Last Updated on STN: 22 Feb 2002

```
=> d his

     (FILE 'HOME' ENTERED AT 16:59:27 ON 19 APR 2004)

     FILE 'MEDLINE, USPATFULL, DGENE, WPIDS, BIOSIS, FSTA, BIOBUSINESS'
     ENTERED AT 17:03:29 ON 19 APR 2004
L1         93950 S ATM OR ATAXIA TELANGIECTASIS
L2        114238 S P53
L3          6648 S ATR
L4           302 S L2 AND L3
L5            90 S L4 AND INHIBIT
L6             0 S L4 AND INHIBIT INTERACTION
L7            64 S L5 AND COMPOUND
L8            59 S L7 AND PEPTIDE
L9           302 S L3 AND L2
L10         1284 S L1 AND L2
L11          297 S L10 AND INHIBIT
L12            1 S L11 AND INHIBIT INTERACTION
L13          237 S L11 AND COMPOUND
L14          199 S L13 AND PEPTIDE
L15        17472 S ASSAY METHOD
L16            0 S ATM () P53 () INHIBIT
L17            0 S ATR () P53 () INHIBIT
L18            0 S ATM () P53 () INTERACTION
L19            0 S INHIBIT ATM AN P53
L20           14 S INHIBIT ATM AND P53
L21         5813 S ATM AND INHIBIT
L22          575 S ATR AND INHIBIT
L23            9 S ATM INHIBITION
L24            3 S ATR INHIBITION

=> s p53 inhibition
L25          122 P53 INHIBITION

=> s l21 and l22
L26          130 L21 AND L22

=> s l126 and l25
L126 NOT FOUND
The L-number entered could not be found.  To see the definition
of L-numbers, enter DISPLAY HISTORY at an arrow prompt (=>).

=> s l26 and l25
L27            0 L26 AND L25

=> d l25 ti abs ibib 1-10

L25  ANSWER 1 OF 122     MEDLINE on STN
TI   Impairment of p53 acetylation, stability and function by an oncogenic
     transcription factor.
AB   Mutations of p53 are remarkably rare in acute promyelocytic leukemias
```

(APLs). Here, we demonstrate that the APL-associated fusion proteins PML-RAR and PLZF-RAR directly inhibit p53, allowing leukemic blasts to evade p53-dependent cancer surveillance pathways. PML-RAR causes deacetylation and degradation of p53, resulting in repression of p53 transcriptional activity, and protection from p53-dependent responses to genotoxic stress. These phenomena are dependent on the expression of wild-type PML, acting as a bridge between p53 and PML-RAR. Recruitment of histone deacetylase (HDAC) to p53 and inhibition of p53 activity were abrogated by conditions that either inactivate HDACs or trigger HDAC release from the fusion protein, implicating recruitment of HDAC by PML-RAR as the mechanism underlying **p53 inhibition**.

ACCESSION NUMBER: 2004119242 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 14976551
TITLE: Impairment of p53 acetylation, stability and function by an oncogenic transcription factor.
AUTHOR: Insinga Alessandra; Monestiroli Silvia; Ronzoni Simona; Carbone Roberta; Pearson Mark; Pruneri Giancarlo; Viale Giuseppe; Appella Ettore; Pelicci PierGiuseppe; Minucci Saverio
CORPORATE SOURCE: Department of Experimental Oncology, European Institute of Oncology, Milan, Italy.
SOURCE: EMBO journal, (2004 Mar 10) 23 (5) 1144-54.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-DATA-REVIEW; IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20040311
Last Updated on STN: 20040311

L25 ANSWER 2 OF 122 MEDLINE on STN
TI MDM2 and promyelocytic leukemia antagonize each other through their direct interaction with p53.
AB p53 can be regulated through post-translational modifications and through interactions with positive and negative regulatory factors. MDM2 binding inhibits p53 and promotes its degradation by the proteasome, whereas promyelocytic leukemia (PML) activates p53 by recruiting it to multiprotein complexes termed PML-nuclear bodies. We reported previously an in vivo and in vitro interaction between PML and MDM2 that is independent of p53. In the current study, we investigated whether interaction between MDM2 and PML can indirectly affect p53 activity. Increasing amounts of MDM2 inhibited p53 activation by PML but could not inhibit PML-mediated activation of a p53 fusion protein that lacked the MDM2-binding domain. Conversely, increasing amounts of PML could overcome **p53 inhibition** by MDM2 but could not overcome MDM2-mediated inhibition of a p53 fusion protein that lacked the PML-binding domain. These results demonstrate that MDM2 and PML can antagonize each other through their direct interaction with p53 and suggest the combined effects of MDM2 and PML on p53 function are determined by the relative level of each protein. Furthermore, these results imply that interactions between MDM2 and PML by themselves have little or no effect on p53 activity.

ACCESSION NUMBER: 2003568402 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14507915
TITLE: MDM2 and promyelocytic leukemia antagonize each other through their direct interaction with p53.
AUTHOR: Zhu Hongyan; Wu Liqing; Maki Carl G
CORPORATE SOURCE: Department of Radiation Oncology, University of Chicago, Chicago, Illinois 60611, USA.
SOURCE: Journal of biological chemistry, (2003 Dec 5) 278 (49) 49286-92.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200403
ENTRY DATE: Entered STN: 20031216
Last Updated on STN: 20040311
Entered Medline: 20040310

L25 ANSWER 3 OF 122 MEDLINE on STN
TI PTEN reverses MDM2-mediated chemotherapy resistance by interacting with p53 in acute lymphoblastic leukemia cells.
AB The tumor suppressor PTEN has been associated with the cellular localization of MDM2 in regulation of apoptosis through inhibiting PI3k/Akt signaling. To investigate whether expression of PTEN is involved in MDM2-mediated chemoresistance, we examined a set of acute lymphoblastic leukemia (ALL) cell lines for the expression of PTEN and sensitivity to doxorubicin. Testing 9 ALL cell lines selected for wild-type p53 phenotype and uniformly high levels of MDM2 expression, we initially demonstrated that cell lines with high levels of PTEN expression were sensitive to doxorubicin, whereas lines lacking PTEN expression were generally resistant. Forced expression of PTEN in a PTEN-negative and doxorubicin-resistant ALL line (EU-1) resulted in decreased cell growth and enhanced sensitivity to doxorubicin. Examining the cellular localization of MDM2, we confirmed that the majority of MDM2 is localized in the nucleus in PTEN-negative doxorubicin-sensitive ALL cells, whereas MDM2 is expressed predominantly in the cytoplasm in either PTEN-positive or PTEN-transfected cells. Furthermore, by coimmunoprecipitaton and cotransfection assays, we found that PTEN physically binds p53 in vitro as well as in vivo. Binding of PTEN to p53 attenuated MDM2-mediated **p53 inhibition**. These results suggest that PTEN inhibits MDM2 and protects p53 through both p13k/Akt-dependent and -independent pathways. Furthermore, loss of PTEN can result in resistance to apoptosis by activating MDM2-mediated antiapoptotic mechanism.
ACCESSION NUMBER: 2003480837 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14559824
TITLE: PTEN reverses MDM2-mediated chemotherapy resistance by interacting with p53 in acute lymphoblastic leukemia cells.
AUTHOR: Zhou Muxiang; Gu Lubing; Findley Harry W; Jiang Rong; Woods William G
CORPORATE SOURCE: Division of Pediatric Hematology/Oncology/Bone Marrow Transplantation, Emory University School of Medicine, 2040 Ridgewood Drive N.E., Atlanta, GA 30322, USA.. mzhou@emory.edu
CONTRACT NUMBER: CA 82323 (NCI)
SOURCE: Cancer research, (2003 Oct 1) 63 (19) 6357-62. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 20031016
Last Updated on STN: 20031219
Entered Medline: 20031203

L25 ANSWER 4 OF 122 MEDLINE on STN
TI p53-dependent cell death signaling in neurons.
AB The p53 tumor suppressor gene is a sequence-specific transcription factor that activates the expression of genes engaged in promoting growth arrest or cell death in response to multiple forms of cellular stress. p53 expression is elevated in damaged neurons in acute models of injury such as ischemia and epilepsy and in brain tissue samples derived from animal models and patients with chronic neurodegenerative diseases. p53 deficiency or **p53 inhibition** protects neurons from a wide variety of acute toxic insults. Signal transduction pathways

associated with p53-induced neuronal cell death are being characterized, suggesting that intervention may prove effective in maintaining neuronal viability and restoring function following neural injury and disease.

ACCESSION NUMBER: 2003076373 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12587660
TITLE: p53-dependent cell death signaling in neurons.
AUTHOR: Morrison Richard S; Kinoshita Yoshito; Johnson Mark D; Guo Weiqun; Garden Gwenn A
CORPORATE SOURCE: Department of Neurological Surgery, University of Washington School of Medicine, Seattle, Washington 98195-6470, USA.. yael@u.washington.edu
SOURCE: Neurochemical research, (2003 Jan) 28 (1) 15-27. Ref: 143
Journal code: 7613461. ISSN: 0364-3190.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20030218
Last Updated on STN: 20030416
Entered Medline: 20030411

L25 ANSWER 5 OF 122 MEDLINE on STN
TI iASPP oncoprotein is a key inhibitor of p53 conserved from worm to human.
AB We have previously shown that ASPP1 and ASPP2 are specific activators of p53; one mechanism by which wild-type p53 is tolerated in human breast carcinomas is through loss of ASPP activity. We have further shown that 53BP2, which corresponds to a C-terminal fragment of ASPP2, acts as a dominant negative inhibitor of p53 (reference 1). Hence, an inhibitory form of ASPP resembling 53BP2 could allow cells to bypass the tumor-suppressor functions of p53 and the ASPP proteins. Here, we characterize such a protein, iASPP (inhibitory member of the ASPP family), encoded by PPP1R13L in humans and ape-1 in Caenorhabditis elegans. iASPP is an evolutionarily conserved inhibitor of **p53**; **inhibition** of iASPP by RNA-mediated interference or antisense RNA in C. elegans or human cells, respectively, induces p53-dependent apoptosis. Moreover, iASPP is an oncoprotein that cooperates with Ras, E1A and E7, but not mutant p53, to transform cells in vitro. Increased expression of iASPP also confers resistance to ultraviolet radiation and to cisplatin-induced apoptosis. iASPP expression is upregulated in human breast carcinomas expressing wild-type p53 and normal levels of ASPP. Inhibition of iASPP could provide an important new strategy for treating tumors expressing wild-type p53.

ACCESSION NUMBER: 2003050693 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12524540
TITLE: iASPP oncoprotein is a key inhibitor of p53 conserved from worm to human.
AUTHOR: Bergamaschi Daniele; Samuels Yardena; O'Neil Nigel J; Trigiante Giuseppe; Crook Tim; Hsieh Jung-Kuang; O'Connor Daniel J; Zhong Shan; Campargue Isabelle; Tomlinson Matthew L; Kuwabara Patricia E; Lu Xin
CORPORATE SOURCE: Ludwig Institute for Cancer Research, Imperial College School of Medicine, St. Mary's Campus, Norfolk Place, London, W2 1PG, UK.
SOURCE: Nature genetics, (2003 Feb) 33 (2) 162-7.
Journal code: 9216904. ISSN: 1061-4036.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20030202

Last Updated on STN: 20030305
Entered Medline: 20030304

L25 ANSWER 6 OF 122 MEDLINE on STN

TI Reporter gene transactivation by human p53 is inhibited in thioredoxin reductase null yeast by a mechanism associated with thioredoxin oxidation and independent of changes in the redox state of glutathione.

AB Reporter gene transactivation by human p53 is compromised in S. cerevisiae lacking the TRR1 gene encoding thioredoxin reductase. The basis for **p53 inhibition** was investigated by measuring the redox state of thioredoxin and glutathione in wild-type and Deltatrr1 yeast. The Deltatrr1 mutation affected the redox state of both molecules. About 34% of thioredoxin was in the disulfide form in wild-type yeast and increased to 70% in Deltatrr1 yeast. About 18% of glutathione was in the GSSG form in wild-type yeast and increased to 32% in Deltatrr1 yeast. The Deltatrr1 mutation also resulted in a 2.9-fold increase in total glutathione per mg extract protein. Highcopy expression of the GLR1 gene encoding glutathione reductase in Deltatrr1 yeast restored the GSSG:GSH ratio to wild-type levels, but did not restore p53 activity. Also, p53 activity was shown to be unaffected by a Deltaglr1 mutation, even though the mutation was known to result in glutathione oxidation. In summary, the results show that, although glutathione becomes more oxidized in Deltatrr1 cells, glutathione oxidation is neither sufficient nor necessary for **p53 inhibition**. The results indicate that p53 activity has a specific requirement for an intact thioredoxin system, rather than a general dependence on the intracellular reducing environment.

ACCESSION NUMBER: 2002643406 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12376468
TITLE: Reporter gene transactivation by human p53 is inhibited in thioredoxin reductase null yeast by a mechanism associated with thioredoxin oxidation and independent of changes in the redox state of glutathione.
AUTHOR: Merwin J R; Mustacich D J; Muller E G D; Pearson G D; Merrill G F
CORPORATE SOURCE: Molecular and Cellular Biology Program, Oregon State University, Corvallis, Oregon 97331, USA.
CONTRACT NUMBER: CA82633 (NCI)
SOURCE: Carcinogenesis, (2002 Oct) 23 (10) 1609-15.
Journal code: 8008055. ISSN: 0143-3334.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20021030
Last Updated on STN: 20021211
Entered Medline: 20021122

L25 ANSWER 7 OF 122 MEDLINE on STN

TI Acceleration of cutaneous wound healing by transient **p53 inhibition**.

AB The increase of cell proliferation during early wound healing is thought to be regulated by a decrease of apoptosis. In contrast, the reduction of cellularity during final wound maturation may be controlled by an increase of apoptotic cell death. Herein we studied whether p53 is involved in wound healing-associated apoptosis and whether transient inhibition of p53 is effective to improve the early healing process of cutaneous wounds. Using intravital microscopic and immunohistochemical techniques in hairless mice, we demonstrated that in vivo inhibition of p53 by pifithrin-alpha (PFT-alpha; 2.2 mg/kg ip) accelerates early epithelialization and neovascularization of cutaneous wounds by (i) promoting leukocyte recruitment, (ii) increasing cell proliferation, and (iii) reducing apoptotic cell death. We further show that final wound

closure with down-regulation of cell proliferation is not inhibited by PFT-alpha treatment, indicating that transient blockade of p53 function does not affect the process of wound maturation. Western blot analysis revealed that PFT-alpha lowered nuclear but not cytoplasmic p53, implying that cytoplasmic retention of p53 mediates the antiapoptotic effects of PFT-alpha. Furthermore, PFT-alpha significantly increased expression of proliferating cell nuclear antigen protein in whole extracts of cutaneous tissue and caused a rise in proliferation of wild-type, but not mutant, p53-expressing keratinocytes. From our study we conclude that transient inhibition of p53 supports the early cell proliferation required for rapid tissue repair and that this may represent an attractive approach in the treatment of delayed wound healing.

ACCESSION NUMBER: 2002422314 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12177245
TITLE: Acceleration of cutaneous wound healing by transient **p53 inhibition.**
AUTHOR: Vollmar B; El-Gibaly A M; Scheuer C; Strik M W; Bruch H-P; Menger M D
CORPORATE SOURCE: Institute for Clinical and Experimental Surgery, University of Saarland, Homburg/Saar, Germany.. exbvol@uniklinik-saarland.de
SOURCE: Laboratory investigation; a journal of technical methods and pathology, (2002 Aug) 82 (8) 1063-71. Journal code: 0376617. ISSN: 0023-6837.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020815
Last Updated on STN: 20020831
Entered Medline: 20020830

L25 ANSWER 8 OF 122 MEDLINE on STN
TI Accumulation of an inactive form of p53 protein in cells treated with TNF alpha.
AB In MCF-7 cells, TNF alpha induces a G1 arrest with an increased expression of p21/Waf1, an activation of NF-kappa B and an accumulation of p53. NF-kappa B and p53 are two transcriptional factors known to activate p21/Waf1 gene expression. Here we show that **p53 inhibition** has no effect on p21/Waf1 mRNA accumulation following TNF alpha treatment. In contrast, inactivation of NF-kappa B inhibits p21/Waf1 expression without affecting G1 arrest. The fact that p21/Waf1 gene expression is still stimulated when p53 is inactivated strongly suggests that TNF alpha induces accumulation of an inactive form of p53 protein. This assumption was further supported by the following observations: (i) the p53 DNA-binding activity to its consensus sequence was not stimulated following TNF alpha treatment, (ii) phosphorylation at Ser-15, -20 or -392 was not detected in response to TNF alpha, (iii) the transcription rate of Ddb2, another p53 target gene, was not stimulated by TNF alpha. Finally, the accumulation of p53 in the nuclei of TNF alpha-treated MCF-7 cells was concomitant with an increase in p53 mRNA level, suggesting a regulation at the transcription level.

ACCESSION NUMBER: 2002235348 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11973611
TITLE: Accumulation of an inactive form of p53 protein in cells treated with TNF alpha.
AUTHOR: Drane P; Leblanc V; Miro-Mur F; Saffroy R; Debuire B; May E
CORPORATE SOURCE: Commissariat a l'Energie Atomique, Laboratoire de Cancerogenese Moleculaire, UMR217 CEA-CNRS, DRR, DSV, BP6 92265 Fontenay-aux-Roses Cedex, France.
SOURCE: Cell death and differentiation, (2002 May) 9 (5) 527-37. Journal code: 9437445. ISSN: 1350-9047.
PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020426
Last Updated on STN: 20020829
Entered Medline: 20020828

L25 ANSWER 9 OF 122 MEDLINE on STN
TI Pifithrin-alpha, an inhibitor of p53, enhances the genetic instability induced by etoposide (VP16) in human lymphoblastoid cells treated in vitro.
AB Recent studies indicate that p53-dependent apoptosis induced in normal tissues during chemo- and radiotherapy can cause severe side effects of anti-cancer treatments that limit their efficiency.The aim of the present work was to further characterise the role of p53 in maintaining genomic stability and to verify whether the inhibition of p53 function in normal cells by pifithrin-alpha (PFT-alpha) may contribute in reducing the side effects of cancer therapy. Two human lymphoblastoid cell lines, derived from the same donor, TK6 (p53 wild type) and WTK1 (p53 mutated) have been treated with an anti-neoplastic drug, the etoposide (VP16), an inhibitor of DNA topoisomerase II in presence or in absence of the p53 inhibitor PFT-alpha. Following treatments with VP16 on TK6 and WTK1, we observed a higher induction of chromosome aberrations in WTK1 (p53 mutated) and of apoptosis in TK6 (p53 wild-type) cells. The **p53 inhibition** by PFT-alpha in VP16 treated TK6 cells produced an increase of chromosomal aberrations and a reduction of apoptosis. Therefore, the temporary suppression of the function of p53 by PFT-alpha, increasing the survival of the normal cells, could be a promising approach to reduce the side-effects of cancer therapy but it is important to consider that the surviving cells could be genetically modified and consequently the risk of secondary tumours could be increased.
ACCESSION NUMBER: 2002140470 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11827710
TITLE: Pifithrin-alpha, an inhibitor of p53, enhances the genetic instability induced by etoposide (VP16) in human lymphoblastoid cells treated in vitro.
AUTHOR: Bassi L; Carloni M; Fonti E; Palma de la Pena N; Meschini R; Palitti F
CORPORATE SOURCE: Dipartimento di Agrobiologia e Agrochimica, Universita' degli Studi della Tuscia, Via San Camillo De Lellis, 01100, Viterbo, Italy.
SOURCE: Mutation research, (2002 Feb 20) 499 (2) 163-76.
Journal code: 0400763. ISSN: 0027-5107.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020307
Last Updated on STN: 20020322
Entered Medline: 20020321

L25 ANSWER 10 OF 122 MEDLINE on STN
TI ATR is not required for p53 activation but synergizes with p53 in the replication checkpoint.
AB ATR (ataxia telangiectasia and Rad-3-related) is a protein kinase required for survival after DNA damage. A critical role for ATR has been hypothesized to be the regulation of p53 and other cell cycle checkpoints. ATR has been shown to phosphorylate p53 at Ser(15), and this damage-induced phosphorylation is diminished by expression of a catalytically inactive (ATR-kd) mutant. p53 function could not be examined directly in prior studies of ATR, however, because p53 was mutant or because cells expressed the SV40 large T antigen that blocks p53 function.

To test the interactions of ATR and p53 directly we generated human U2OS cell lines inducible for either wild-type or kinase-dead ATR that also have an intact p53 pathway. Indeed, ATR-kd expression sensitized these cells to DNA damage and caused a transient decrease in damage-induced serine 15 phosphorylation of p53. However, we found that the effects of ATR-kd expression do not result in blocking the response of p53 to DNA damage. Specifically, prior ATR-kd expression had no effect on DNA damage-induced p53 protein up-regulation, p53-DNA binding, p21 mRNA up-regulation, or G(1) arrest. Instead of promoting survival via p53 regulation, we found that ATR protects cells by delaying the generation of mitotic phosphoproteins and inhibiting premature chromatin condensation after DNA damage or hydroxyurea. Although **p53 inhibition** (by E6 or MDM2 expression) had little effect on premature chromatin condensation, when combined with ATR-kd expression there was a marked loss of the replication checkpoint. We conclude that ATR and p53 can function independently but that loss of both leads to synergistic disruption of the replication checkpoint.

ACCESSION NUMBER: 2002096134 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11711532
TITLE: ATR is not required for p53 activation but synergizes with p53 in the replication checkpoint.
AUTHOR: Nghiem Paul; Park Peter K; Kim Ys Yong-son; Desai Bimal N; Schreiber Stuart L
CORPORATE SOURCE: Department of Chemistry, Howard Hughes Medical Institute, Harvard University, Cambridge, Massachusetts 02138, USA.
CONTRACT NUMBER: GM-52067 (NIGMS)
K08-AR0208703 (NIAMS)
SOURCE: Journal of biological chemistry, (2002 Feb 8) 277 (6) 4428-34.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020205
Last Updated on STN: 20030105
Entered Medline: 20020305

=> d his

(FILE 'HOME' ENTERED AT 16:59:27 ON 19 APR 2004)

FILE 'MEDLINE, USPATFULL, DGENE, WPIDS, BIOSIS, FSTA, BIOBUSINESS'
ENTERED AT 17:03:29 ON 19 APR 2004

```
L1        93950 S ATM OR ATAXIA TELANGIECTASIS
L2       114238 S P53
L3         6648 S ATR
L4          302 S L2 AND L3
L5           90 S L4 AND INHIBIT
L6            0 S L4 AND INHIBIT INTERACTION
L7           64 S L5 AND COMPOUND
L8           59 S L7 AND PEPTIDE
L9          302 S L3 AND L2
L10        1284 S L1 AND L2
L11         297 S L10 AND INHIBIT
L12           1 S L11 AND INHIBIT INTERACTION
L13         237 S L11 AND COMPOUND
L14         199 S L13 AND PEPTIDE
L15       17472 S ASSAY METHOD
L16           0 S ATM () P53 () INHIBIT
L17           0 S ATR () P53 () INHIBIT
L18           0 S ATM () P53 () INTERACTION
```

```
L19           0 S INHIBIT ATM AN P53
L20          14 S INHIBIT ATM AND P53
L21        5813 S ATM AND INHIBIT
L22         575 S ATR AND INHIBIT
L23           9 S ATM INHIBITION
L24           3 S ATR INHIBITION
L25         122 S P53 INHIBITION
L26         130 S L21 AND L22
L27           0 S L26 AND L25

=> d l26 ti abs ibib 1-10

L26  ANSWER 1 OF 130     MEDLINE on STN
TI   Selective inhibition of the DNA-dependent protein kinase (DNA-PK) by the
     radiosensitizing agent caffeine.
AB   Caffeine inhibits cell cycle checkpoints, sensitizes cells to ionizing
     radiation-induced cell killing and inhibits the protein kinase activity of
     two cell cycle checkpoint regulators, Ataxia-Telangiectasia mutated (
     ATM) and ATM- and Rad3-related (ATR).  In
     contrast, caffeine has been reported to have little effect on the protein
     kinase activity of the DNA-dependent protein kinase (DNA-PK), which is
     essential for the repair of DNA double-strand breaks.  Previously, we
     reported that DNA-PK phosphorylates Thr21 of the 32 kDa subunit of
     replication protein A (RPA32) in response to camptothecin.  In this report
     we demonstrate that the camptothecin-induced phosphorylation of RPA32 on
     Thr21 is inhibited by 2 mM caffeine.  In addition, we show that caffeine
     inhibits immunoprecipitated and purified DNA-PK, as well as DNA-PK in cell
     extracts, with an IC50 of 0.2-0.6 mM.  Caffeine inhibited DNA-PK activity
     through a mixed non-competitive mechanism with respect to ATP.  In
     contrast, 10-fold higher concentrations of caffeine were required to
     inhibit DNA-PK autophosphorylation in vitro and caffeine failed to
     inhibit DNA-PKcs dependent double-strand break repair in vivo.
     These data suggest that while DNA-PK does not appear to be the target of
     caffeine-induced radiosensitization, caffeine cannot be used to
     differentiate between ATM, ATR and DNA- PK-dependent
     substrate phosphorylation in vivo.
ACCESSION NUMBER:   2004187648     IN-PROCESS
DOCUMENT NUMBER:    PubMed ID: 15060176
TITLE:              Selective inhibition of the DNA-dependent protein kinase
                    (DNA-PK) by the radiosensitizing agent caffeine.
AUTHOR:             Block Wesley D; Merkle Dennis; Meek Katheryn; Lees-Miller
                    Susan P
CORPORATE SOURCE:   Department of Biological Sciences, Cancer Biology Research
                    Group, University of Calgary, 3330 Hospital Drive N.W.,
                    Calgary AB, T2N 4N1, Canada.
SOURCE:             Nucleic acids research, (2004) 32 (6) 1967-72.
                    Journal code: 0411011. ISSN: 1362-4962.
PUB. COUNTRY:       England: United Kingdom
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE:         Entered STN: 20040416
                    Last Updated on STN: 20040416

L26  ANSWER 2 OF 130     MEDLINE on STN
TI   Inhibition of DNA repair by Pentoxifylline and related methylxanthine
     derivatives.
AB   The methylxanthine drug Pentoxifylline is reviewed for new properties
     which have emerged only relatively recently and for which clinical
     applications can be expected.  After a summary on the established systemic
     effects of Pentoxifylline on the microcirculation and reduction of tumour
     anoxia, the role of the drug in the treatment of vasoocclusive disorders,
     cerebral ischemia, infectious diseases, septic shock and acute respiratory
     distress, the review focuses on another level of drug action which is
```

based on in vitro observations in a variety of cell lines. Pentoxifylline and the related drug Caffeine are known radiosensitizers especially in p53 mutant cells. The explanation that the drug abrogates the G2 block and shortens repair in G2 by promoting early entry into mitosis is not anymore tenable because enhancement of radiotoxicity requires presence of the drug during irradiation and fails when the drug is added after irradiation at the G2 maximum. Repair assays by measurement of recovery ratios and by delayed plating experiments indeed strongly suggested a role in repair which is now confirmed for Pentoxifylline by constant field gel electrophoresis (CFGE) measurements and for Pentoxifylline and for Caffeine by use of a variety of repair mutants. The picture now emerging shows that Caffeine and Pentoxifylline **inhibit** homologous recombination by targeting members of the PIK kinase family (**ATM** and **ATR**) which facilitate repair in G2. Pentoxifylline induced repair inhibition between irradiation dose fractions to counter interfraction repair has been successfully applied in a model for stereotactic surgery. Another realistic avenue of application of Pentoxifylline in tumour therapy comes from experiments which show that repair events in G2 can be targeted directly by addition of cytotoxic drugs and Pentoxifylline at the G2 maximum. Under these conditions massive dose enhancement factors of up to 80 have been observed suggesting that it may be possible to realise dramatic improvements to tumour growth control in the clinic.

ACCESSION NUMBER: 2003523173 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14599774
TITLE: Inhibition of DNA repair by Pentoxifylline and related methylxanthine derivatives.
AUTHOR: Bohm Lothar; Roos Wynand Paul; Serafin Antonio Mendes
CORPORATE SOURCE: Department of Pharmacology, Faculty of Health Sciences, University of Stellenbosch, P.O. Box 19063, 7505 Tygerberg, South Africa.. elb@sun.ac.za
SOURCE: Toxicology, (2003 Nov 15) 193 (1-2) 153-60. Ref: 72
Journal code: 0361055. ISSN: 0300-483X.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 20031106
Last Updated on STN: 20031217
Entered Medline: 20031216

L26 ANSWER 3 OF 130 MEDLINE on STN
TI DNA damage checkpoint control in cells exposed to ionizing radiation.
AB Damage induced in the DNA after exposure of cells to ionizing radiation activates checkpoint pathways that **inhibit** progression of cells through the G1 and G2 phases and induce a transient delay in the progression through S phase. Checkpoints together with repair and apoptosis are integrated in a circuitry that determines the ultimate response of a cell to DNA damage. Checkpoint activation typically requires sensors and mediators of DNA damage, signal transducers and effectors. Here, we review the current state of knowledge regarding mechanisms of checkpoint activation and proteins involved in the different steps of the process. Emphasis is placed on the role of **ATM** and **ATR**, as well on CHK1 and CHK2 kinases in checkpoint response. The roles of downstream effectors, such as P53 and the CDC25 family of proteins, are also described, and connections between repair and checkpoint activation are attempted. The role of checkpoints in genomic stability and the potential of improving the treatment of cancer by DNA damage inducing agents through checkpoint abrogation are also briefly outlined.

ACCESSION NUMBER: 2003408354 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12947390
TITLE: DNA damage checkpoint control in cells exposed to ionizing radiation.
AUTHOR: Iliakis George; Wang Ya; Guan Jun; Wang Huichen
CORPORATE SOURCE: Institute of Medical Radiation Biology, University of Essen Medical School, Hufelanstrasse 55, 45122 Essen, Germany.. Georg.Iliakis@uni-essen.de
CONTRACT NUMBER: 2P01 CA56690 (NCI)
CA42026 (NCI)
CA56706 (NCI)
CA76203 (NCI)
SOURCE: Oncogene, (2003 Sep 1) 22 (37) 5834-47.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030830
Last Updated on STN: 20031002
Entered Medline: 20031001

L26 ANSWER 4 OF 130 MEDLINE on STN
TI Protein kinase inhibitor 2-aminopurine overrides multiple genotoxic stress-induced cellular pathways to promote cell survival.
AB 2-Aminopurine (2-AP) is an adenine analog shown to cause cells to bypass chemical- and radiation-induced cell cycle arrest through as-yet unidentified mechanisms. 2-AP has also been shown to act as a kinase inhibitor. Tumor suppressor p53 plays an important role in the control of cell cycle and apoptosis in response to genotoxic stress. We were interested in examining the effect of 2-AP on p53 phosphorylation and its possible consequences on checkpoint control in cells subjected to various forms of DNA damage. Here, we show that 2-AP suppresses p53 phosphorylation in response to gamma radiation, adriamycin, or ultraviolet treatment. This is partly explained by the ability of the kinase inhibitor to **inhibit ATM** or **ATR** activities in vitro and impair **ATM**- or **ATR**-dependent p53 phosphorylation in vivo. However, 2-AP is also capable of inhibiting p53 phosphorylation in cells deficient in **ATM**, DNA-PK, or **ATR** suggesting the existence of multiple pathways by which this kinase inhibitor modulates p53 activation. Biologically, the 2-AP-mediated inhibition of p53 stabilization enables wild-type p53-containing cells to bypass adriamycin-induced G(2)/M arrest. In the long term, however, 2-AP facilitates cells to resist DNA damage-induced cell death independently of p53.
ACCESSION NUMBER: 2003275742 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12802279
TITLE: Protein kinase inhibitor 2-aminopurine overrides multiple genotoxic stress-induced cellular pathways to promote cell survival.
AUTHOR: Huang Shirley; Qu Li-Ke; Cuddihy Andrew R; Ragheb Rafik; Taya Yoichi; Koromilas Antonis E
CORPORATE SOURCE: Department of Microbiology and Immunology, McGill University, Montreal, Canada H3A 2T5.
SOURCE: Oncogene, (2003 Jun 12) 22 (24) 3721-33.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030613
Last Updated on STN: 20030703
Entered Medline: 20030702

L26 ANSWER 5 OF 130 MEDLINE on STN

TI Enhanced radiation and chemotherapy-mediated cell killing of human cancer cells by small inhibitory RNA silencing of DNA repair factors.

AB Recent developments in the use of small inhibitory RNA molecules (siRNAs) to **inhibit** specific protein expression have highlighted the potential use of siRNA as a therapeutic agent. The double-strand break signaling/repair proteins **ATM**, **ATR**, and DNA-dependent protein kinase catalytic subunit (DNA-PK(cs)) are attractive targets to confer enhanced radio and chemosensitivity to tumor cells. We have designed and exogenously delivered plasmids encoding siRNAs targeting these critical kinases to human cancer cells to assess the feasibility of this concept as a clinically translatable experimental therapeutic. siRNA led to a approximately 90% reduction in target protein expression. siRNAs targeting **ATM** and DNA-PK(cs) gave rise to a dose-reduction factor of approximately 1.4 compared with untransfected and control vector-transfected cells at the clinically relevant radiation doses. This was greater than the radiosensitivity achieved using the phosphatidylinositol 3'-kinase inhibitor Wortmannin or DNA-PK(cs) competitive inhibitor LY294002. A similar increased sensitivity to the alkylating agent methyl methanesulfonate (MMS) was also observed for siRNA-mediated **ATR** silencing. Together, these data provide strong evidence for the potential use of siRNA as a novel radiation/chemotherapy-sensitizing agent.

ACCESSION NUMBER: 2003154270 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12670903
TITLE: Enhanced radiation and chemotherapy-mediated cell killing of human cancer cells by small inhibitory RNA silencing of DNA repair factors.
AUTHOR: Collis Spencer J; Swartz Michael J; Nelson William G; DeWeese Theodore L
CORPORATE SOURCE: Department of Radiation Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21231, USA.
SOURCE: Cancer research, (2003 Apr 1) 63 (7) 1550-4. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20030403
Last Updated on STN: 20030423
Entered Medline: 20030422

L26 ANSWER 6 OF 130 MEDLINE on STN

TI Defective S phase chromatin assembly causes DNA damage, activation of the S phase checkpoint, and S phase arrest.

AB The S phase checkpoint protects the genome from spontaneous damage during DNA replication, although the cause of damage has been unknown. We used a dominant-negative mutant of a subunit of CAF-I, a complex that assembles newly synthesized DNA into nucleosomes, to **inhibit** S phase chromatin assembly and found that this induced S phase arrest. Arrest was accompanied by DNA damage and S phase checkpoint activation and required **ATR** or **ATM** kinase activity. These results show that in human cells CAF-I activity is required for completion of S phase and that a defect in chromatin assembly can itself induce DNA damage. We propose that errors in chromatin assembly, occurring spontaneously or caused by genetic mutations or environmental agents, contribute to genome instability.

ACCESSION NUMBER: 2003108496 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12620223
TITLE: Defective S phase chromatin assembly causes DNA damage, activation of the S phase checkpoint, and S phase arrest.
COMMENT: Comment in: Mol Cell. 2003 Feb;11(2):283-4. PubMed ID:

12620214
AUTHOR: Ye Xiaofen; Franco Alexa A; Santos Hidelita; Nelson David M; Kaufman Paul D; Adams Peter D
CORPORATE SOURCE: Division of Basic Science, Fox Chase Cancer Center, Philadelphia, PA 19111, USA.
CONTRACT NUMBER: 1R01 GM55712 (NIGMS)
R01 -GM62281 (NIGMS)
SOURCE: Molecular cell, (2003 Feb) 11 (2) 341-51.
Journal code: 9802571. ISSN: 1097-2765.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20030307
Last Updated on STN: 20030403
Entered Medline: 20030402

L26 ANSWER 7 OF 130 MEDLINE on STN
TI **ATR** regulates fragile site stability.
AB Conditions that partially **inhibit** DNA replication induce expression of common fragile sites. These sites form gaps and breaks on metaphase chromosomes and are deleted and rearranged in many tumors. Yet, the mechanism of fragile site expression has been elusive. We demonstrate that the replication checkpoint kinase **ATR**, but not **ATM**, is critical for maintenance of fragile site stability. **ATR** deficiency results in fragile site expression with and without addition of replication inhibitors. Thus, we propose that fragile sites are unreplicated chromosomal regions resulting from stalled forks that escape the **ATR** replication checkpoint. These findings have important implications for understanding both the mechanism of fragile site instability and the consequences of stalled replication in mammalian cells.
ACCESSION NUMBER: 2003020404 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12526805
TITLE: **ATR** regulates fragile site stability.
AUTHOR: Casper Anne M; Nghiem Paul; Arlt Martin F; Glover Thomas W
CORPORATE SOURCE: Department of Human Genetics, University of Michigan, Ann Arbor, MI 48109, USA.
CONTRACT NUMBER: CA43222 (NCI)
GM38627 (NIGMS)
K08-AR02087 (NIAMS)
SOURCE: Cell, (2002 Dec 13) 111 (6) 779-89.
Journal code: 0413066. ISSN: 0092-8674.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20030116
Last Updated on STN: 20030225
Entered Medline: 20030224

L26 ANSWER 8 OF 130 MEDLINE on STN
TI G2 DNA damage checkpoint inhibition and antimitotic activity of 13-hydroxy-15-oxozoapatlin.
AB Checkpoints activated in response to DNA damage cause arrest in the G(1) and G(2) phases of the cell cycle. Inhibitors of the G(2) checkpoint may be used as tools to study this response and also to increase the effectiveness of DNA-damaging therapies against cancers lacking p53 function. Using a cell-based assay for G(2) checkpoint inhibitors, we have screened extracts from the NCI National Institutes of Health Natural Products Repository and have identified 13-hydroxy-15-oxozoapatlin (OZ) from the African tree Parinari curatellifolia. Flow cytometry with a

mitosis-specific antibody showed that checkpoint inhibition by OZ was maximal at 10 microm, which released 20% of irradiated MCF-7 cells expressing defective p53 and 30% of irradiated HCT116p53(-/-) cells from G(2) arrest. OZ additively increased the response to the checkpoint inhibitors isogranulatimide and debromohymenialdisine, but it did not augment the effects of UCN-01 or caffeine. Unlike other checkpoint inhibitors, OZ did not **inhibit** ataxia-telangiectasia mutated (**ATM**), **ATM** and Rad3-related (**ATR**), Chk1, Chk2, Plk1, or Ser/Thr protein phosphatases in vitro. Treatment with OZ also caused G(2)-arrested and cycling cells to arrest in mitosis in a state resembling prometaphase. In these cells, the chromosomes were condensed and scattered over disordered mitotic spindles. The results demonstrate that OZ is both a G(2) checkpoint inhibitor and an antimitotic agent.

ACCESSION NUMBER: 2002046807 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11572854
TITLE: G2 DNA damage checkpoint inhibition and antimitotic activity of 13-hydroxy-15-oxozoapatlin.
AUTHOR: Rundle N T; Xu L; Andersen R J; Roberge M
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of British Columbia, Vancouver, British Columbia V6T 1Z3, Canada.
SOURCE: Journal of biological chemistry, (2001 Dec 21) 276 (51) 48231-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20030105
Entered Medline: 20020131

L26 ANSWER 9 OF 130 MEDLINE on STN
TI **ATR** inhibition selectively sensitizes G1 checkpoint-deficient cells to lethal premature chromatin condensation.
AB Premature chromatin condensation (PCC) is a hallmark of mammalian cells that begin mitosis before completing DNA replication. This lethal event is prevented by a highly conserved checkpoint involving an unknown, caffeine-sensitive mediator. Here, we have examined the possible involvement of the caffeine-sensitive **ATM** and **ATR** protein kinases in this checkpoint. We show that caffeine's ability to **inhibit ATR** (but not **ATM**) causes PCC, that **ATR** (but not **ATM**) prevents PCC, and that **ATR** prevents PCC via Chk-1 regulation. Moreover, mimicking cancer cell phenotypes by disrupting normal G(1) checkpoints sensitizes cells to PCC by **ATR** inhibition plus low-dose DNA damage. Notably, loss of p53 function potently sensitizes cells to PCC caused by **ATR** inhibition by a small molecule. We present a molecular model for how **ATR** prevents PCC and suggest that **ATR** represents an attractive therapeutic target for selectively killing cancer cells by premature chromatin condensation.

ACCESSION NUMBER: 2001445854 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11481475
TITLE: **ATR** inhibition selectively sensitizes G1 checkpoint-deficient cells to lethal premature chromatin condensation.
AUTHOR: Nghiem P; Park P K; Kim Y; Vaziri C; Schreiber S L
CORPORATE SOURCE: Department of Chemistry and Chemical Biology, Howard Hughes Medical Institute, Harvard University, Cambridge, MA 02138, USA.
CONTRACT NUMBER: GM-52067 (NIGMS)
K08-AR0208703 (NIAMS)
SOURCE: Proceedings of the National Academy of Sciences of the

United States of America, (2001 Jul 31) 98 (16) 9092-7.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010903
Entered Medline: 20010830

L26 ANSWER 10 OF 130 MEDLINE on STN
TI Regulation of the G2/M transition by p53.
AB p53 protects mammals from neoplasia by inducing apoptosis, DNA repair and cell cycle arrest in response to a variety of stresses. p53-dependent arrest of cells in the G1 phase of the cell cycle is an important component of the cellular response to stress. Here we review recent evidence that implicates p53 in controlling entry into mitosis when cells enter G2 with damaged DNA or when they are arrested in S phase due to depletion of the substrates required for DNA synthesis. Part of the mechanism by which p53 blocks cells at the G2 checkpoint involves inhibition of Cdc2, the cyclin-dependent kinase required to enter mitosis. Cdc2 is inhibited simultaneously by three transcriptional targets of p53, Gadd45, p21, and 14-3-3 sigma. Binding of Cdc2 to Cyclin B1 is required for its activity, and repression of the cyclin B1 gene by p53 also contributes to blocking entry into mitosis. p53 also represses the cdc2 gene, to help ensure that cells do not escape the initial block. Genotoxic stress also activates p53-independent pathways that **inhibit** Cdc2 activity, activation of the protein kinases Chk1 and Chk2 by the protein kinases **Atm** and **Atr**. Chk1 and Chk2 **inhibit** Cdc2 by inactivating Cdc25, the phosphatase that normally activates Cdc2. Chk1, Chk2, **Atm** and **Atr** also contribute to the activation of p53 in response to genotoxic stress and therefore play multiple roles. p53 induces transcription of the reprimo, B99, and mcg10 genes, all of which contribute to the arrest of cells in G2, but the mechanisms of cell cycle arrest by these genes is not known. Repression of the topoisomerase II gene by p53 helps to block entry into mitosis and strengthens the G2 arrest. In summary, multiple overlapping p53-dependent and p53-independent pathways regulate the G2/M transition in response to genotoxic stress.
ACCESSION NUMBER: 2001237339 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11313928
TITLE: Regulation of the G2/M transition by p53.
AUTHOR: Taylor W R; Stark G R
CORPORATE SOURCE: Department of Molecular Biology, Lerner Research Insititute, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA.
CONTRACT NUMBER: GM49345 (NIGMS)
SOURCE: Oncogene, (2001 Apr 5) 20 (15) 1803-15. Ref: 126
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010503

```
L9          302 S L3 AND L2
L10        1284 S L1 AND L2
L11         297 S L10 AND INHIBIT
L12           1 S L11 AND INHIBIT INTERACTION

=> d l11 ti abs ibib 1-10

L11  ANSWER 1 OF 297     MEDLINE on STN
TI   Relationship between the radiosensitizing effect of wortmannin, DNA
     double-strand break rejoining, and p21WAF1 induction in human normal and
     tumor-derived cells.
AB   Wortmannin (WM) is a potent inhibitor of the catalytic sub-unit of DNA-PK,
     which is involved in one pathway of DNA double-strand break (DSB)
     rejoining, and of ATM, which functions upstream in the
     p53 signaling pathway.  WM is known to be an efficient
     radiosensitizer in a variety of mammalian cell types, to inhibit
     DSB rejoining following exposure to supralethal doses (> or =30 Gy) of
     ionizing radiation, and to abrogate the induction of p53 at
     early times after radiation exposure.  We report here that WM is a more
     effective radiosensitizer in A549 human lung carcinoma cells than in
     normal human fibroblasts (NHFs).  In addition, WM strongly inhibits DSB
     rejoining in A549 cells exposed to relatively low doses (e.g., 10 Gy) of
     ionizing radiation, without having any detectable effect in NHFs.  We
     further demonstrate that WM significantly potentiates the induction of
     p21WAF1, a p53-regulated gene that encodes for a key mediator of
     cell-cycle/growth arrest, when determined at late times (e.g., 24 h) after
     irradiation.  This late WM-dependent potentiation of p21WAF1 induction
     following radiation exposure is observed in NHFs and in the p53
     wild-type tumor cell lines A549, A172, and SKNSH, but not in the
     p53-deficient tumor cell lines DLD-1, HeLa, and SKNSH-E6.  We
     conclude that: (i) inhibition of DSB rejoining by WM may be an important
     contributor to its radiosensitizing effect in A549 cells but not in NHFs;
     and (ii) radiosensitization of p53-proficient human cells by WM
     may in part be associated with the delayed induction of p21WAF1, which can
     lead to a sustained growth-arrested phenotype resembling senescence.
     Copyright 2004 Wiley-Liss, Inc.
ACCESSION NUMBER:   2004101117     IN-PROCESS
DOCUMENT NUMBER:    PubMed ID: 14991746
TITLE:              Relationship between the radiosensitizing effect of
                    wortmannin, DNA double-strand break rejoining, and p21WAF1
                    induction in human normal and tumor-derived cells.
AUTHOR:             Mirzayans Razmik; Pollock Scott; Scott April; Enns Louise;
                    Andrais Bonnie; Murray David
CORPORATE SOURCE:   Department of Oncology, University of Alberta, Cross Cancer
                    Institute, Edmonton, Alberta, Canada.
SOURCE:             Molecular carcinogenesis, (2004 Mar) 39 (3) 164-72.
                    Journal code: 8811105. ISSN: 0899-1987.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE:         Entered STN: 20040302
                    Last Updated on STN: 20040320

L11  ANSWER 2 OF 297     MEDLINE on STN
TI   Inhibition of DNA repair by Pentoxifylline and related methylxanthine
     derivatives.
AB   The methylxanthine drug Pentoxifylline is reviewed for new properties
     which have emerged only relatively recently and for which clinical
     applications can be expected.  After a summary on the established systemic
     effects of Pentoxifylline on the microcirculation and reduction of tumour
     anoxia, the role of the drug in the treatment of vasoocclusive disorders,
     cerebral ischemia, infectious diseases, septic shock and acute respiratory
     distress, the review focuses on another level of drug action which is
```

based on in vitro observations in a variety of cell lines. Pentoxifylline and the related drug Caffeine are known radiosensitizers especially in **p53** mutant cells. The explanation that the drug abrogates the G2 block and shortens repair in G2 by promoting early entry into mitosis is not anymore tenable because enhancement of radiotoxicity requires presence of the drug during irradiation and fails when the drug is added after irradiation at the G2 maximum. Repair assays by measurement of recovery ratios and by delayed plating experiments indeed strongly suggested a role in repair which is now confirmed for Pentoxifylline by constant field gel electrophoresis (CFGE) measurements and for Pentoxifylline and for Caffeine by use of a variety of repair mutants. The picture now emerging shows that Caffeine and Pentoxifylline **inhibit** homologous recombination by targeting members of the PIK kinase family (**ATM** and ATR) which facilitate repair in G2. Pentoxifylline induced repair inhibition between irradiation dose fractions to counter interfraction repair has been successfully applied in a model for stereotactic surgery. Another realistic avenue of application of Pentoxifylline in tumour therapy comes from experiments which show that repair events in G2 can be targeted directly by addition of cytotoxic drugs and Pentoxifylline at the G2 maximum. Under these conditions massive dose enhancement factors of up to 80 have been observed suggesting that it may be possible to realise dramatic improvements to tumour growth control in the clinic.

ACCESSION NUMBER: 2003523173 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14599774
TITLE: Inhibition of DNA repair by Pentoxifylline and related methylxanthine derivatives.
AUTHOR: Bohm Lothar; Roos Wynand Paul; Serafin Antonio Mendes
CORPORATE SOURCE: Department of Pharmacology, Faculty of Health Sciences, University of Stellenbosch, P.O. Box 19063, 7505 Tygerberg, South Africa.. elb@sun.ac.za
SOURCE: Toxicology, (2003 Nov 15) 193 (1-2) 153-60. Ref: 72
Journal code: 0361055. ISSN: 0300-483X.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 20031106
Last Updated on STN: 20031217
Entered Medline: 20031216

L11 ANSWER 3 OF 297 MEDLINE on STN
TI **ATM**'s leucine-rich domain and adjacent sequences are essential for **ATM** to regulate the DNA damage response.
AB The **ATM** protein kinase regulates the DNA damage response by phosphorylating proteins involved in cell cycle checkpoints and DNA repair. We report here on the function of the predicted leucine zipper (LZ) motif, and sequences adjacent to this, in regulating **ATM** activity. The predicted LZ sequence was deleted from **ATM**, generating ATMDeltaLZ, and expressed in an **ATM**-negative AT cell line. **ATM** increased cell survival following exposure to ionizing radiation, whereas expression of ATMDeltaLZ failed to increase cell survival. ATMDeltaLZ retained in vitro kinase activity, but was unable to phosphorylate **p53** in vivo. Leucine zippers mediate homo- and heterodimerization of proteins. However, the predicted LZ of **ATM** did not mediate the formation of **ATM** dimers. We examined if the predicted LZ of **ATM** was a dominant-negative inhibitor of **ATM** function in SW480 cells. Expression of amino acids 769-1436 of **ATM**, including the predicted LZ, sensitized SW480 cells to ionizing radiation, but did not **inhibit** **ATM**'s kinase activity or its ability to phosphorylate Brca1. Further, this dominant-negative activity was not dependent on the

predicted LZ domain. The central region of the **ATM** protein therefore contains multiple sequences which regulate cell survival following DNA damage.

ACCESSION NUMBER: 2003447610 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14508513
TITLE: **ATM**'s leucine-rich domain and adjacent sequences are essential for **ATM** to regulate the DNA damage response.
AUTHOR: Chen Shujuan; Paul Proma; Price Brendan D
CORPORATE SOURCE: Department of Radiation Oncology, JF513, Dana-Farber Cancer Institute, Harvard Medical School, 44 Binney Street, Boston, MA 02115, USA.
CONTRACT NUMBER: CA64585 (NCI)
CA93602 (NCI)
SOURCE: Oncogene, (2003 Sep 25) 22 (41) 6332-9.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030926
Last Updated on STN: 20031024
Entered Medline: 20031023

L11 ANSWER 4 OF 297 MEDLINE on STN
TI DNA damage checkpoint control in cells exposed to ionizing radiation.
AB Damage induced in the DNA after exposure of cells to ionizing radiation activates checkpoint pathways that **inhibit** progression of cells through the G1 and G2 phases and induce a transient delay in the progression through S phase. Checkpoints together with repair and apoptosis are integrated in a circuitry that determines the ultimate response of a cell to DNA damage. Checkpoint activation typically requires sensors and mediators of DNA damage, signal transducers and effectors. Here, we review the current state of knowledge regarding mechanisms of checkpoint activation and proteins involved in the different steps of the process. Emphasis is placed on the role of **ATM** and ATR, as well on CHK1 and CHK2 kinases in checkpoint response. The roles of downstream effectors, such as **P53** and the CDC25 family of proteins, are also described, and connections between repair and checkpoint activation are attempted. The role of checkpoints in genomic stability and the potential of improving the treatment of cancer by DNA damage inducing agents through checkpoint abrogation are also briefly outlined.

ACCESSION NUMBER: 2003408354 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12947390
TITLE: DNA damage checkpoint control in cells exposed to ionizing radiation.
AUTHOR: Iliakis George; Wang Ya; Guan Jun; Wang Huichen
CORPORATE SOURCE: Institute of Medical Radiation Biology, University of Essen Medical School, Hufelanstrasse 55, 45122 Essen, Germany.. Georg.Iliakis@uni-essen.de
CONTRACT NUMBER: 2P01 CA56690 (NCI)
CA42026 (NCI)
CA56706 (NCI)
CA76203 (NCI)
SOURCE: Oncogene, (2003 Sep 1) 22 (37) 5834-47.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030830

Last Updated on STN: 20031002
Entered Medline: 20031001

L11 ANSWER 5 OF 297 MEDLINE on STN
TI Protein kinase inhibitor 2-aminopurine overrides multiple genotoxic stress-induced cellular pathways to promote cell survival.
AB 2-Aminopurine (2-AP) is an adenine analog shown to cause cells to bypass chemical- and radiation-induced cell cycle arrest through as-yet unidentified mechanisms. 2-AP has also been shown to act as a kinase inhibitor. Tumor suppressor **p53** plays an important role in the control of cell cycle and apoptosis in response to genotoxic stress. We were interested in examining the effect of 2-AP on **p53** phosphorylation and its possible consequences on checkpoint control in cells subjected to various forms of DNA damage. Here, we show that 2-AP suppresses **p53** phosphorylation in response to gamma radiation, adriamycin, or ultraviolet treatment. This is partly explained by the ability of the kinase inhibitor to **inhibit ATM** or ATR activities in vitro and impair **ATM**- or ATR-dependent **p53** phosphorylation in vivo. However, 2-AP is also capable of inhibiting **p53** phosphorylation in cells deficient in **ATM**, DNA-PK, or ATR suggesting the existence of multiple pathways by which this kinase inhibitor modulates **p53** activation. Biologically, the 2-AP-mediated inhibition of **p53** stabilization enables wild-type **p53**-containing cells to bypass adriamycin-induced G(2)/M arrest. In the long term, however, 2-AP facilitates cells to resist DNA damage-induced cell death independently of **p53**.
ACCESSION NUMBER: 2003275742 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12802279
TITLE: Protein kinase inhibitor 2-aminopurine overrides multiple genotoxic stress-induced cellular pathways to promote cell survival.
AUTHOR: Huang Shirley; Qu Li-Ke; Cuddihy Andrew R; Ragheb Rafik; Taya Yoichi; Koromilas Antonis E
CORPORATE SOURCE: Department of Microbiology and Immunology, McGill University, Montreal, Canada H3A 2T5.
SOURCE: Oncogene, (2003 Jun 12) 22 (24) 3721-33.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030613
Last Updated on STN: 20030703
Entered Medline: 20030702

L11 ANSWER 6 OF 297 MEDLINE on STN
TI Mechanisms of resistance to rapamycins.
AB Rapamycins represent a novel family of anticancer agents, currently including rapamycin and its derivatives, CCI-779 and RAD001. Rapamycins **inhibit** the function of the mammalian target of rapamycin (mTOR), and potently suppress tumor cell growth by arresting cells in G1 phase or potentially inducing apoptosis of cells, in culture or in xenograft tumor models. However, recent data indicate that genetic mutations or compensatory changes in tumor cells influence the sensitivity of rapamycins. First, mutations of mTOR or FKBP12 prevent rapamycin from binding to mTOR, conferring rapamycin resistance. Second, mutations or defects of mTOR-regulated proteins, including S6K1, 4E-BP1, PP2A-related phosphatases, and p27(Kip1) also render rapamycin insensitivity. In addition, the status of **ATM**, **p53**, PTEN/Akt and 14-3-3 are also associated with rapamycin sensitivity. To better explore the role of rapamycins against tumors, this review will summarize the current knowledge of the mechanism of action of rapamycins, and progress in understanding mechanisms of acquired or intrinsic resistance.

ACCESSION NUMBER: 2002291626 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12030785
TITLE: Mechanisms of resistance to rapamycins.
AUTHOR: Huang S; Houghton P J
CORPORATE SOURCE: Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, TN 38105-2794, USA.
CONTRACT NUMBER: CA23099 (NCI)
CA28765 (NCI)
CA77776 (NCI)
SOURCE: Drug resistance updates : reviews and commentaries in antimicrobial and anticancer chemotherapy, (2001 Dec) 4 (6) 378-91. Ref: 126
Journal code: 9815369. ISSN: 1368-7646.
PUB. COUNTRY: Scotland: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020529
Last Updated on STN: 20020801
Entered Medline: 20020731

L11 ANSWER 7 OF 297 MEDLINE on STN
TI G2 DNA damage checkpoint inhibition and antimitotic activity of 13-hydroxy-15-oxozoapatlin.
AB Checkpoints activated in response to DNA damage cause arrest in the G(1) and G(2) phases of the cell cycle. Inhibitors of the G(2) checkpoint may be used as tools to study this response and also to increase the effectiveness of DNA-damaging therapies against cancers lacking **p53** function. Using a cell-based assay for G(2) checkpoint inhibitors, we have screened extracts from the NCI National Institutes of Health Natural Products Repository and have identified 13-hydroxy-15-oxozoapatlin (OZ) from the African tree Parinari curatellifolia. Flow cytometry with a mitosis-specific antibody showed that checkpoint inhibition by OZ was maximal at 10 microm, which released 20% of irradiated MCF-7 cells expressing defective **p53** and 30% of irradiated HCT116p53(-/-) cells from G(2) arrest. OZ additively increased the response to the checkpoint inhibitors isogranulatimide and debromohymenialdisine, but it did not augment the effects of UCN-01 or caffeine. Unlike other checkpoint inhibitors, OZ did not **inhibit** ataxia-telangiectasia mutated (**ATM**), **ATM** and Rad3-related (ATR), Chk1, Chk2, Plk1, or Ser/Thr protein phosphatases in vitro. Treatment with OZ also caused G(2)-arrested and cycling cells to arrest in mitosis in a state resembling prometaphase. In these cells, the chromosomes were condensed and scattered over disordered mitotic spindles. The results demonstrate that OZ is both a G(2) checkpoint inhibitor and an antimitotic agent.
ACCESSION NUMBER: 2002046807 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11572854
TITLE: G2 DNA damage checkpoint inhibition and antimitotic activity of 13-hydroxy-15-oxozoapatlin.
AUTHOR: Rundle N T; Xu L; Andersen R J; Roberge M
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of British Columbia, Vancouver, British Columbia V6T 1Z3, Canada.
SOURCE: Journal of biological chemistry, (2001 Dec 21) 276 (51) 48231-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20030105
Entered Medline: 20020131

L11 ANSWER 8 OF 297 MEDLINE on STN
TI **ATM** as a target for novel radiosensitizers.
AB DNA damage checkpoints are complex signal transduction pathways that are critical for normal cellular recovery following potentially lethal genotoxic insults. The ataxia-telangiectasia mutated (**ATM**) protein kinase is a critical component in these pathways and integrates the cellular response to damage by phosphorylating key proteins involved in cell cycle regulation and DNA repair. Lack of normal **ATM** function in the inherited ataxia-telangiectasia (A-T) syndrome results in a pleiotropic clinical syndrome characterized by a marked increased risk of cancer and profound hypersensitivity to ionizing radiation. Cells derived from patients with A-T share some of these attributes with genomic instability, loss of normal cell cycle arrest pathways, defects in DNA repair and increased radiation sensitivity. The radiosensitivity of A-T cells suggests that pharmacological inhibitors of the **ATM** kinase should be effective radiosensitizing agents. In fact, caffeine inhibits **ATM** kinase activity at concentrations that result in an A-T-like phenotype with loss of cell cycle checkpoints and hypersensitivity to ionizing radiation. Although the clinical use of caffeine as a radiosensitizer is limited by potentially lethal systemic toxicities, more potent methyl xanthines may selectively **inhibit** the **ATM** pathway at clinically achievable levels. Interestingly, caffeine and other methyl xanthines preferentially radiosensitize cells that lack normal **p53** function. Because **p53** is commonly inactivated in epithelial malignancies, this suggests that small molecule inhibitors of **ATM** might selectively sensitize the majority of tumors to the lethal effects of ionizing radiation while sparing normal tissues.

ACCESSION NUMBER: 2001571421 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11677656
TITLE: **ATM** as a target for novel radiosensitizers.
AUTHOR: Sarkaria J N; Eshleman J S
CORPORATE SOURCE: Department of Oncology, Mayo Foundation, Rochester, MN 55905, USA.
CONTRACT NUMBER: CA80829 (NCI)
SOURCE: Seminars in radiation oncology, (2001 Oct) 11 (4) 316-27.
Ref: 100
Journal code: 9202882. ISSN: 1053-4296.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011029
Last Updated on STN: 20020123
Entered Medline: 20011207

L11 ANSWER 9 OF 297 MEDLINE on STN
TI ATR inhibition selectively sensitizes G1 checkpoint-deficient cells to lethal premature chromatin condensation.
AB Premature chromatin condensation (PCC) is a hallmark of mammalian cells that begin mitosis before completing DNA replication. This lethal event is prevented by a highly conserved checkpoint involving an unknown, caffeine-sensitive mediator. Here, we have examined the possible involvement of the caffeine-sensitive **ATM** and ATR protein

```
Connecting via Winsock to STN


Welcome to STN International!  Enter x:x

LOGINID:ssspta1653hxp

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  JAN 27   Source of Registration (SR) information in REGISTRY updated
                   and searchable
 NEWS  4  JAN 27   A new search aid, the Company Name Thesaurus, available in
                   CA/CAplus
 NEWS  5  FEB 05   German (DE) application and patent publication number format
                   changes
 NEWS  6  MAR 03   MEDLINE and LMEDLINE reloaded
 NEWS  7  MAR 03   MEDLINE file segment of TOXCENTER reloaded
 NEWS  8  MAR 03   FRANCEPAT now available on STN
 NEWS  9  MAR 29   Pharmaceutical Substances (PS) now available on STN
 NEWS 10  MAR 29   WPIFV now available on STN
 NEWS 11  MAR 29   No connect hour charges in WPIFV until May 1, 2004
 NEWS 12  MAR 29   New monthly current-awareness alert (SDI) frequency in RAPRA

 NEWS EXPRESS  MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 13 APRIL 2004
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN Customer
  agreement.  Please note that this agreement limits use to scientific
  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 12:41:32 ON 19 APR 2004

=> FIL STNGUIDE
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'STNGUIDE' ENTERED AT 12:41:43 ON 19 APR 2004
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE
```

```
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Apr 16, 2004 (20040416/UP).

=> FIL HOME
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY     SESSION
FULL ESTIMATED COST                                         0.06        0.27

FILE 'HOME' ENTERED AT 12:41:47 ON 19 APR 2004

=> file medline, uspatful, dgene, fsta, wpids
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY     SESSION
FULL ESTIMATED COST                                         1.26        1.53

FILE 'MEDLINE' ENTERED AT 12:45:13 ON 19 APR 2004

FILE 'USPATFULL' ENTERED AT 12:45:13 ON 19 APR 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'DGENE' ENTERED AT 12:45:13 ON 19 APR 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE 'FSTA' ENTERED AT 12:45:13 ON 19 APR 2004
COPYRIGHT (C) 2004 International Food Information Service

FILE 'WPIDS' ENTERED AT 12:45:13 ON 19 APR 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

=> s ATM
L1        89011 ATM

=> DNA-PK
DNA-PK IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s DNA-PK
L2          906 DNA-PK

=> s ATR
L3         5043 ATR

=> s l1 and l2
L4          227 L1 AND L2

=> s l4 and l3
L5          108 L4 AND L3

=> s p53
L6        76499 P53

=> s l6 and l5
L7           66 L6 AND L5

=> s l7 and assay
L8           47 L7 AND ASSAY

=> s l8 and method
L9           24 L8 AND METHOD

=> d l9 ti abs ibib tot
```

L9 ANSWER 1 OF 24 USPATFULL on STN
TI Drug screening systems and assays
AB A **method** of stimulating non-homologous end-joining (NHEJ) of DNA the **method** comprising performing NHEJ of DNA in the presence of inositol hexakisphosphate (IP.sub.6) or other stimulatory inositol phosphate. An **assay** of a protein kinase wherein the **assay** comprises inositol hexakisphosphate (IP.sub.6) or other stimulatory inositol phosphate. The invention also provides screening assays for compounds which may modulate NHEJ and which may be therapeutically useful; and screening assays for compounds which may modulate **DNA-PK** and related protein kinases and which may be therapeutically useful. Methods of modulating NHEJ and protein kinases are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2004:38591 USPATFULL			
TITLE:	Drug screening systems and assays			
INVENTOR(S):	West, Steve Craig, South Mimms Hertfordshire, UNITED KINGDOM Bartlett-Jones, Michael, London, UNITED KINGDOM Akemi Hanakahi, Leslyn Ann, Baltimore, MD, UNITED STATES			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004029130	A1	20040212	
APPLICATION INFO.:	US 2003-296014	A1	20030612	(10)
	WO 2001-GB2180		20010518	
	NUMBER		DATE	
PRIORITY INFORMATION:	GB 2000-12179		20000520	
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
LEGAL REPRESENTATIVE:	FISH & RICHARDSON PC, 225 FRANKLIN ST, BOSTON, MA, 02110			
NUMBER OF CLAIMS:	56			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	18 Drawing Page(s)			
LINE COUNT:	2260			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 2 OF 24 USPATFULL on STN
TI Methods for detecting dna damage and screening for cancer therapeutics
AB A **method** for detecting DNA damage in a tissue sample involves contacting an immobilized biological sample with a labeled ligand which binds to human 53Bp1, and examining the immobilized sample for the presence of a label generated-detectable signal concentrated in foci in said sample. The presence of concentrated foci is indicative of DNA damage and the presence of diffuse signal is indicative of a normal sample. Diagnostic reagents contain a ligand that binds to human 53Bp1 associated with a detectable label. Diagnostic kits for detecting DNA damage in a biological sample contain such diagnostic reagents and signal detection components. Compositions that inhibit or antagonize the biological activity of 53Bp1 are identified by suitable assays, and are employed in methods of retarding the growth of a cancer cell.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2004:31097 USPATFULL
TITLE:	Methods for detecting dna damage and screening for cancer therapeutics
INVENTOR(S):	Halazonetis, Thanos, Wynnewood, PA, UNITED STATES Schultz, Linda B., Suwanee, GA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004023235	A1	20040205	
APPLICATION INFO.:	US 2003-276312	A1	20030117	(10)
	WO 2001-US17471		20010530	

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-60208716	20000601

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HOWSON AND HOWSON, ONE SPRING HOUSE CORPORATION CENTER, BOX 457, 321 NORRISTOWN ROAD, SPRING HOUSE, PA, 19477
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 2295
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 3 OF 24 USPATFULL on STN
TI **ATM** inhibitors
AB The application concerns a compound of formula I: ##STR1##

wherein one of P and Q is O, and the other of P and Q is CH, where there is a double bond between whichever of Q and P is CH and the carbon atom bearing the R.sup.3 group;

Y is either O or S;

R.sup.1 and R.sup.2 are independently hydrogen, an optionally substituted C.sub.1-7 alkyl group, C.sub.3-20 heterocyclyl group, or C.sub.5-20 aryl group, or may together form an optionally substituted heterocyclic ring having from 4 to 8 ring atoms;

R.sup.3 is a phenyl or pyridyl group, attached by a first bridge group selected from --S--, --S(.dbd.O)--, --S(.dbd.O).sub.2--, --O--, --NR.sup.N-- and CR.sup.C1R.sup.C2-- to an optionally substituted C.sub.5-20 carboaryl group, the phenyl or pyridyl group and optionally substituted C.sub.5-20 carboaryl group being optionally further linked by a second bridge group, so as to form an optionally substituted C.sub.5-7 ring, the phenyl or pyridyl group being further optionally substituted.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2004:2469 USPATFULL
TITLE: **ATM** inhibitors
INVENTOR(S): Murray Smith, Graeme Cameron, Cambridge, UNITED KINGDOM
Barr Martin, Niall Morrison, Cambridge, UNITED KINGDOM
Jackson, Stephen Philip, Cambridge, UNITED KINGDOM
O'Connor, Mark James, Cambridge, UNITED KINGDOM
Kai Lau, Alan Yin, Cambridge, UNITED KINGDOM
Cockcroft, Xiao-Ling Fan, Horsham, UNITED KINGDOM
Williams Matthews, Ian Timothy, Horsham, UNITED KINGDOM
Menear, Keith Allan, Horsham, UNITED KINGDOM
Martin Rigoreau, Laurent Jean, Horsham, UNITED KINGDOM
Hummersone, Marc Geoffery, Horsham, UNITED KINGDOM
Griffin, Roger John, Morpeth, UNITED KINGDOM
PATENT ASSIGNEE(S): Kudos Pharmaceuticals Ltd, Cambridge, UNITED KINGDOM (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004002492	A1	20040101	
APPLICATION INFO.:	US 2003-373114	A1	20030224	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	GB 2002-4350	20020225
	US 2002-360493P	20020228 (60)
	US 2002-395884P	20020715 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MICHAEL BEST & FRIEDRICH, LLP, ONE SOUTH PINCKNEY STREET, P O BOX 1806, MADISON, WI, 53701
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 3199
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 4 OF 24 USPATFULL on STN
TI **ATM** related kinase ATX, nucleic acids encoding same and methods of use
AB The invention provides an isolated nucleic acid molecule having substantially the same nucleotide sequence as SEQ ID NO:1. Also provided is an isolated oligonucleotide having at least 15 contiguous nucleotides of a nucleotide sequence referenced as SEQ ID NO:11. An isolated polypeptide having substantially the same amino acid sequence as SEQ ID NO:2 is further provided as well as an antibody, or antigen binding fragment thereof, which specifically binds to an ATX polypeptide and has an amino acid sequence as referenced in SEQ ID NO:2. A **method** for identifying an ATX-modulatory compound is additionally provided. The **method** consists of measuring the level of an ATX polypeptide in the presence of a test compound, wherein a difference in the level of said ATX polypeptide in the presence of said test compound compared to in the absence of said test compound indicating that said test compound is an ATX-modulatory compound, and wherein said ATX-modulatory compound is not caffeine or wortmannin.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:324700 USPATFULL
TITLE: **ATM** related kinase ATX, nucleic acids encoding same and methods of use
INVENTOR(S): Abraham, Robert T., San Diego, CA, UNITED STATES
Otterness, Diane M., San Diego, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003228675	A1	20031211
APPLICATION INFO.:	US 2002-165216	A1	20020606 (10)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CAMPBELL & FLORES LLP, 4370 LA JOLLA VILLAGE DRIVE, 7TH FLOOR, SAN DIEGO, CA, 92122
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 18 Drawing Page(s)
LINE COUNT: 6825
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 5 OF 24 USPATFULL on STN
TI Cancer models
AB The invention provides chimeric non-human animals, methods for making and using chimeric non-human animals, isolated stem cells, and methods for identifying agents that reduces cancer in a non-human animal. For example, the invention relates to using stem cells to make chimeric non-human animals having cancer or the ability to develop cancer. Such animals can be used to evaluate tumorigenesis, tumor maintenance, and

tumor regression in vivo. In addition, the chimeric non-human animals provided herein can be used to identify agents that reduce or prevent tumor formation or growth in vivo.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2003:320406 USPATFULL		
TITLE:	Cancer models		
INVENTOR(S):	Bachoo, Robert M., Roslindale, MA, UNITED STATES Depinho, Ronald A., Brookline, MA, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003226159	A1	20031204
APPLICATION INFO.:	US 2003-414460	A1	20030415 (10)
	NUMBER		DATE
PRIORITY INFORMATION:	US 2002-373139P		20020416 (60)
	US 2002-374791P		20020422 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	FISH & RICHARDSON PC, 225 FRANKLIN ST, BOSTON, MA, 02110		
NUMBER OF CLAIMS:	29		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	6 Drawing Page(s)		
LINE COUNT:	1230		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 6 OF 24 USPATFULL on STN

TI Novel human protein kinases and protein kinase-like enzymes

AB The present invention relates to kinase polypeptides, nucleotide sequences encoding the kinase polypeptides, as well as various products and methods useful for the diagnosis and treatment of various kinase-related diseases and conditions. Through the use of a bioinformatics strategy, mammalian members of the PTK's and STK's have been identified and their protein structure predicted.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2003:300763 USPATFULL		
TITLE:	Novel human protein kinases and protein kinase-like enzymes		
INVENTOR(S):	Plowman, Gregory D, San Carlos, CA, UNITED STATES Whyte, David, Belmont, CA, UNITED STATES Manning, Gerard, Menlo Park, CA, UNITED STATES Sudarsanam, Sucha, Greenbrae, CA, UNITED STATES Martinez, Ricardo, Foster City, CA, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003211989	A1	20031113
APPLICATION INFO.:	US 2003-220955	A1	20030226 (10)
	WO 2001-US6838		20010302
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	FOLEY AND LARDNER, SUITE 500, 3000 K STREET NW, WASHINGTON, DC, 20007		
NUMBER OF CLAIMS:	28		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	16 Drawing Page(s)		
LINE COUNT:	7135		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 7 OF 24 USPATFULL on STN

TI Wortmannin derivatives as probes of cellular proteins and processes

AB One aspect of the present invention relates to methods and reagents for profiling cells and/or subcellular environments (e.g., membrane or nuclear cellular fractions). The invention uses small molecule probes that bind covalently to protein targets, which significantly simplifies purification and identification of proteins using full length or proteolyzed proteins. Proteins, cellular components or other binding partners (collectively known as "LBP" or "lipid binding partner") can be naturally occurring, such as proteins or fragments of proteins cloned or otherwise derived from cells, or can be artificial, e.g., polypeptides which are selected from random or semi-random polypeptide libraries.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:276724 USPATFULL

TITLE: Wortmannin derivatives as probes of cellular proteins and processes

INVENTOR(S): Wandless, Thomas J., Menlo Park, CA, UNITED STATES
Cimprich, Karlene, Menlo Park, CA, UNITED STATES
Chu, Gilbert, Palo Alto, CA, UNITED STATES
Stohlmeyer, Michelle, Chicago, IL, UNITED STATES
Fas, Cornelia, Schwaebisch Gmuend, GERMANY, FEDERAL REPUBLIC OF

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003194749	A1	20031016	
APPLICATION INFO.:	US 2003-368248	A1	20030218	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-357538P	20020215 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: ROPES & GRAY LLP, ONE INTERNATIONAL PLACE, BOSTON, MA, 02110-2624
NUMBER OF CLAIMS: 34
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 3204
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 8 OF 24 USPATFULL on STN

TI Methods and compositions in checkpoint signaling

AB The present invention is directed to compositions and methods regarding the signaling for the presence of DNA damage or replication stress and activating cell cycle checkpoints. Specifically, ATRIP was identified as an interactor with **ATR**, a member of the phosphatidylinositol kinase-related protein family that includes **ATM** and **DNA-PK**. In some embodiments, the present invention is directed to ATRIP and **ATR** acting as mutually dependent partners in cell cycle checkpoint signaling pathways.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:237777 USPATFULL

TITLE: Methods and compositions in checkpoint signaling

INVENTOR(S): Elledge, Stephen J., Houston, TX, UNITED STATES
Cortez, David K., Houston, TX, UNITED STATES
Zou, Lee, Houston, TX, UNITED STATES

PATENT ASSIGNEE(S): Baylor College of Medicine (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003165934	A1	20030904	
APPLICATION INFO.:	US 2002-300453	A1	20021120	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-331821P	20011120 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FULBRIGHT & JAWORSKI, LLP, 1301 MCKINNEY, SUITE 5100, HOUSTON, TX, 77010-3095
NUMBER OF CLAIMS: 74
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Page(s)
LINE COUNT: 7150
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 9 OF 24 USPATFULL on STN
TI **ATM** kinase compositions and methods
AB The present invention provides methods for detecting activation of **ATM** kinase, DNA damage, and DNA damaging agents. Further provided are antibodies which specifically recognize the phosphorylation state of Ataxia Telangiectasia-Mutated (**ATM**) kinase. Methods of identifying agents which modulate the activation and activity of **ATM** kinase are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:225760 USPATFULL
TITLE: **ATM** kinase compositions and methods
INVENTOR(S): Kastan, Michael B., Cordova, TN, UNITED STATES
Bakkenist, Christopher, Cordova, TN, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003157572	A1	20030821
APPLICATION INFO.:	US 2003-351733	A1	20030124 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2002-307077, filed on 27 Nov 2002, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Licata & Tyrrell P.C., 66 E. Main Street, Marlton, NJ, 08053
NUMBER OF CLAIMS: 34
EXEMPLARY CLAIM: 1
LINE COUNT: 1587
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 10 OF 24 USPATFULL on STN
TI Proteomic analysis of tumors for development of consultative report of therapeutic options
AB The present invention provides methods of identifying potential therapeutic options for treatment of a tumor, and a consultative report providing the same.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:180303 USPATFULL
TITLE: Proteomic analysis of tumors for development of consultative report of therapeutic options
INVENTOR(S): Brown, Robert E., Winfield, PA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003124130	A1	20030703
APPLICATION INFO.:	US 2002-325793	A1	20021219 (10)

	NUMBER	DATE

PRIORITY INFORMATION: US 2002-345309P 20020102 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WOODCOCK WASHBURN LLP, ONE LIBERTY PLACE, 46TH FLOOR, 1650 MARKET STREET, PHILADELPHIA, PA, 19103
NUMBER OF CLAIMS: 29
EXEMPLARY CLAIM: 1
LINE COUNT: 970
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 11 OF 24 USPATFULL on STN
TI **ATM** kinase compositions and methods
AB The present invention provides methods for detecting activation of **ATM** kinase, DNA damage, and DNA damaging agents. Further provided are antibodies which specifically recognize the phosphorylation state of Ataxia Telangiectasia-Mutated (**ATM**) kinase. Methods of identifying agents which modulate the activation and activity of **ATM** kinase are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:112929 USPATFULL
TITLE: **ATM** kinase compositions and methods
INVENTOR(S): Kastan, Michael B., Cordova, TN, UNITED STATES
Bakkenist, Christopher, Cordova, TN, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003077661	A1	20030424	
APPLICATION INFO.:	US 2002-307077	A1	20021127	(10)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Jane Massey Licata, Licata & Tyrrell P.C., 66 E. Main Street, Marlton, NJ, 08053
NUMBER OF CLAIMS: 28
EXEMPLARY CLAIM: 1
LINE COUNT: 1890
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 12 OF 24 USPATFULL on STN
TI Compounds useful for inhibiting Chk1
AB Aryl- and heteroaryl-substituted urea compounds useful in the treatment of diseases and conditions related to DNA damage or lesions in DNA replication are disclosed. Methods of making the compounds, and their use as therapeutic agents, for example, in treating cancer and other diseases characterized by defects in DNA replication, chromosome segregation, or cell division also are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:100173 USPATFULL
TITLE: Compounds useful for inhibiting Chk1
INVENTOR(S): Keegan, Kathleen S., Mercer Island, WA, UNITED STATES
Kesicki, Edward A., Bothell, WA, UNITED STATES
Gaudino, John Joseph, Longmont, CO, UNITED STATES
Cook, Adam Wade, Longmont, CO, UNITED STATES
Cowen, Scott Douglas, Longmont, CO, UNITED STATES
Burgess, Laurence Edward, Boulder, CO, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003069284	A1	20030410	
APPLICATION INFO.:	US 2002-87715	A1	20020301	(10)

	NUMBER	DATE

PRIORITY INFORMATION: US 2001-273124P 20010302 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MARSHALL, GERSTEIN & BORUN, 6300 SEARS TOWER, 233 SOUTH WACKER, CHICAGO, IL, 60606-6357
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
LINE COUNT: 6478
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 13 OF 24 USPATFULL on STN
TI **ATM** kinase modulation for screening and therapies
AB The present invention relates to identification of the consensus sequence phosphorylated by **ATM** kinase. This, in turn, permitted identification of **ATM** kinase target proteins, and development of a convenient **assay** system for **ATM** kinase phosphorylation using fusion polypeptides as substrates. The **assay** system is adaptable to screening for **ATM** modulators, particularly inhibitors. In a specific embodiment, the substrate recognition sequence and mutagenized variants of this sequence were incorporated in a GST fusion protein and assayed for phosphorylation by **ATM** kinase. This **assay** system is useful in screening for **ATM** inhibitors. **ATM** function assays were validated using an **ATM**-kinase dead dominant-negative mutant.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:30316 USPATFULL
TITLE: **ATM** kinase modulation for screening and therapies
INVENTOR(S): Kastan, Michael, Cordova, TN, UNITED STATES
Canman, Christine, Cordova, TN, UNITED STATES
Kim, Seong-Tae, Cordova, TN, UNITED STATES
Lim, Dae-Sik, Cordova, TN, UNITED STATES
PATENT ASSIGNEE(S): ST. JUDE CHILDREN'S RESEARCH HOSPITAL (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003022263	A1	20030130
APPLICATION INFO.:	US 2001-24123	A1	20011217 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 1999-400653, filed on 21 Sep 1999, PATENTED Continuation-in-part of Ser. No. US 1999-248061, filed on 10 Feb 1999, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: DARBY & DARBY P.C., 805 Third Avenue, New York, NY, 10022
NUMBER OF CLAIMS: 47
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 3517
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 14 OF 24 USPATFULL on STN
TI Materials and methods to potentiate cancer treatment
AB Compounds that inhibit DNA-dependent protein kinase, compositions comprising the compounds, methods to inhibit the **DNA-PK** biological activity, methods to sensitize cells the agents that cause DNA lesions, and methods to potentiate cancer treatment are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:295172 USPATFULL

TITLE: Materials and methods to potentiate cancer treatment
INVENTOR(S): Halbrook, James, Woodinville, WA, UNITED STATES
Kesicki, Edward A., Bothell, WA, UNITED STATES
Burgess, Laurence E., Boulder, CO, UNITED STATES
Schlachter, Stephen T., Boulder, CO, UNITED STATES
Eary, Charles T., Longmont, CO, UNITED STATES
Schiro, Justin G, Firestone, CO, UNITED STATES
Huang, Hongmei, Broomfield, CO, UNITED STATES
Evans, Michael, Louisville, CO, UNITED STATES
Han, Yongxin, Longmont, CO, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002165218	A1	20021107
APPLICATION INFO.:	US 2001-941897	A1	20010828 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-229899P	20000901 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MARSHALL, GERSTEIN & BORUN, 6300 SEARS TOWER, 233 SOUTH WACKER, CHICAGO, IL, 60606-6357
NUMBER OF CLAIMS: 37
EXEMPLARY CLAIM: 1
LINE COUNT: 5685
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 15 OF 24 USPATFULL on STN
TI Pharmaceutically tractable secondary drug targets, methods of identification and their use in the creation of small molecule therapeutics
AB The present invention relates to a **method** of identifying one or more secondary drug targets and their use in the identification of drug or drug candidates, particularly for the treatment of cancer. The yeast-based synthetic lethal screens were used to functionally identify and validate new gene targets to kill tumor cells with defects in cell cycle checkpoints and damage response pathways. These newly identified gene targets can be used to develop new cancer chemotherapeutics.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:126272 USPATFULL
TITLE: Pharmaceutically tractable secondary drug targets, methods of identification and their use in the creation of small molecule therapeutics
INVENTOR(S): Friend, Stephen, Seattle, WA, UNITED STATES
Hartwell, Leland, Seattle, WA, UNITED STATES
PATENT ASSIGNEE(S): Fred Hutchinson Cancer Research Center (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002064784	A1	20020530
APPLICATION INFO.:	US 2001-847588	A1	20010503 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1998-187229, filed on 6 Nov 1998, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-64657P	19971106 (60)
	US 1998-80471P	19980402 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PATENT ADMINSTRATOR, KATTEN MUCHIN ZAVIS, SUITE 1600,

525 WEST MONROE STREET, CHICAGO, IL, 60661
NUMBER OF CLAIMS: 46
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Page(s)
LINE COUNT: 1358
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 16 OF 24 USPATFULL on STN
TI **ATM** kinase modulation for screening and therapies
AB The present invention relates to identification of the consensus sequence phosphorylated by **ATM** kinase. This, in turn, permitted identification of **ATM** kinase target proteins, and development of a convenient **assay** system for **ATM** kinase phosphorylation using fusion polypeptides as substrates. The **assay** system is adaptable to screening for **ATM** modulators, particularly inhibitors. In a specific embodiment, the substrate recognition sequence and mutagenized variants of this sequence were incorporated in a GST fusion protein and assayed for phosphorylation by **ATM** kinase. This **assay** system is useful in screening for **ATM** inhibitors. **ATM** function assays were validated using an **ATM**-kinase dead dominant-negative mutant.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:108831 USPATFULL
TITLE: **ATM** kinase modulation for screening and therapies
INVENTOR(S): Kastan, Michael, Cordova, TN, United States
Canman, Christine, Cordova, TN, United States
Kim, Seong-Tae, Cordova, TN, United States
Lim, Dae-Sik, Cordova, TN, United States
PATENT ASSIGNEE(S): St. Jude Children's Research Hospital, Memphis, TN, United States (U.S. corporation)
Johns-Hopkins University, Baltimore, MD, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6387640	B1	20020514	
APPLICATION INFO.:	US 1999-248061		19990210	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Achutamurthy, Ponnathapu
ASSISTANT EXAMINER: Monshipouri, M.
LEGAL REPRESENTATIVE: Darby & Darby
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 2258
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 17 OF 24 USPATFULL on STN
TI Compositions and methods for treating neoplastic disease using chemotherapy and radiation sensitizers
AB Inhibitors of KIAA0175 are provided that reduce the expression or biological activities of KIAA0175, **p53** and/or p21 in a mammalian cell. KIAA0175 inhibitors include anti-sense molecules, ribozymes, antibodies and antibody fragments, proteins and polypeptides as well as small molecules. KIAA0175 inhibitors find use in compositions and methods for decreasing KIAA0175, **p53** and/or p21 gene expression as well as methods for increasing the chemo and/or radiosensitivity of mammalian cells, including tumor cells, methods for decreasing the side effects of cancer therapy and methods for treating neoplastic diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:92656 USPATFULL
TITLE:	Compositions and methods for treating neoplastic disease using chemotherapy and radiation sensitizers
INVENTOR(S):	Wu, Bin, El Cerrito, CA, UNITED STATES Seeley, Todd W., Moraga, CA, UNITED STATES Williams, Lewis T., Mill Valley, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002049180	A1	20020425
APPLICATION INFO.:	US 2001-870937	A1	20010530 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-208435P	20000531 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Chiron Corporation, Intellectual Property, P. O. Box 8097, Emeryville, CA, 94662-8097
NUMBER OF CLAIMS:	26
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	1 Drawing Page(s)
LINE COUNT:	1974

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 18 OF 24 USPATFULL on STN

TI **ATM** kinase modulation for screening and therapies

AB The present invention relates to identification of the consensus sequence phosphorylated by **ATM** kinase. This, in turn, permitted identification of **ATM** kinase target proteins, and development of a convenient **assay** system for **ATM** kinase phosphorylation using fusion polypeptides as substrates. The **assay** system is adaptable to screening for **ATM** modulators, particularly inhibitors. In a specific embodiment, the substrate recognition sequence and mutagenized variants of this sequence were incorporated in a GST fusion protein and assayed for phosphorylation by **ATM** kinase. This **assay** system is useful in screening for **ATM** inhibitors. **ATM** function assays were validated using an **ATM**-kinase dead dominant-negative mutant.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:34294 USPATFULL
TITLE:	**ATM** kinase modulation for screening and therapies
INVENTOR(S):	Kastan, Michael, Cordova, TN, United States Canman, Christine, Cordova, TN, United States Kim, Seong-Tae, Cordova, TN, United States Lim, Dae-Sik, Cordova, TN, United States
PATENT ASSIGNEE(S):	St. Jude Childre's Research Hospital, Memphis, TN, United States (U.S. corporation) Johns-Hopkins University, Baltimore, MD, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6348311	B1	20020219
APPLICATION INFO.:	US 1999-400653		19990921 (9)

RELATED APPLN. INFO.:	Continuation of Ser. No. US 1999-248061, filed on 10 Feb 1999
DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED

PRIMARY EXAMINER: Prouty, Rebecca E.
ASSISTANT EXAMINER: Monshipouri, Maryam
LEGAL REPRESENTATIVE: Darby & Darby
NUMBER OF CLAIMS: 2
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 3229
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 19 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assaying phosphorylation enzyme activity on peptide immunologically with antibody to recognize phosphorylated state, useful in screening compounds to control enzyme activities e.g. signal transduction -
AN AAB45783 protein DGENE
AB This invention describes a novel **method** for assaying protein phosphorylation enzyme activity in a sample with DNA-dependent protein kinase, **ATM** or/and **ATR** as the enzyme for phosphorylation. The invention also describes (1) a **method** for screening inhibitors or promoters of the protein phosphorylation enzyme activity comprising: (a) incubation of the enzyme, substrate peptide and a test compound; (b) detecting the level of phosphorylation with an antibody; and (c) comparing the increase or decrease in phosphorylation with that of a control to select the compound; (2) a **method** for assaying dephosphorylation enzyme activity of a protein in a sample as for the phosphorylation **assay**; (3) a **method** for screening inhibitors or promoters of dephosphorylation enzyme activity of a protein carried out in a similar fashion as in (1); (4) an **assay** of DNA-dependent protein kinase activity comprising: (a) determination of the phosphorylation enzyme activity in the absence of a double-stranded DNA; (b) similar determination in presence of the DNA; and (c) comparing (a) and (b) to evaluate phosphorylation enzyme activity originated from the DNA-dependent protein kinase; (5) compounds that can regulate the protein phosphorylation enzyme activity thus screened by any of the methods; (6) an antibody that can recognize the phosphorylated state of a substrate peptide; and (7) an **assay** kit containing the antibody. The **assay** is useful for evaluating the ability of an enzyme to phosphorylate a peptide, which is useful in screening compounds to control enzyme activities e.g. signal transduction.
ACCESSION NUMBER: AAB45783 protein DGENE
TITLE: Assaying phosphorylation enzyme activity on peptide immunologically with antibody to recognize phosphorylated state, useful in screening compounds to control enzyme activities e.g. signal transduction -
INVENTOR: Ogawa A; Kobayashi T; Yano M; Tamai K
PATENT ASSIGNEE: (MEDI-N)MEDICAL & BIOLOGICAL LAB CO LTD.
PATENT INFO: WO 2000072011 A1 20001130 65p
APPLICATION INFO: WO 2000-JP3193 20000518
PRIORITY INFO: JP 1999-141187 19990521
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
OTHER SOURCE: 2001-032064 [04]
DESCRIPTION: Human **p53**-associated peptide fragment SEQ ID NO 9.

L9 ANSWER 20 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assaying phosphorylation enzyme activity on peptide immunologically with antibody to recognize phosphorylated state, useful in screening compounds to control enzyme activities e.g. signal transduction -
AN AAB45782 protein DGENE
AB This invention describes a novel **method** for assaying protein phosphorylation enzyme activity in a sample with DNA-dependent protein kinase, **ATM** or/and **ATR** as the enzyme for phosphorylation. The invention also describes (1) a **method** for screening inhibitors or promoters of the protein phosphorylation enzyme activity comprising: (a) incubation of the enzyme, substrate peptide and

a test compound; (b) detecting the level of phosphorylation with an antibody; and (c) comparing the increase or decrease in phosphorylation with that of a control to select the compound; (2) a **method** for assaying dephosphorylation enzyme activity of a protein in a sample as for the phosphorylation **assay**; (3) a **method** for screening inhibitors or promoters of dephosphorylation enzyme activity of a protein carried out in a similar fashion as in (1); (4) an **assay** of DNA-dependent protein kinase activity comprising: (a) determination of the phosphorylation enzyme activity in the absence of a double-stranded DNA; (b) similar determination in presence of the DNA; and (c) comparing (a) and (b) to evaluate phosphorylation enzyme activity originated from the DNA-dependent protein kinase; (5) compounds that can regulate the protein phosphorylation enzyme activity thus screened by any of the methods; (6) an antibody that can recognize the phosphorylated state of a substrate peptide; and (7) an **assay** kit containing the antibody. The **assay** is useful for evaluating the ability of an enzyme to phosphorylate a peptide, which is useful in screening compounds to control enzyme activities e.g. signal transduction.

ACCESSION NUMBER: AAB45782 protein DGENE
TITLE: Assaying phosphorylation enzyme activity on peptide immunologically with antibody to recognize phosphorylated state, useful in screening compounds to control enzyme activities e.g. signal transduction -
INVENTOR: Ogawa A; Kobayashi T; Yano M; Tamai K
PATENT ASSIGNEE: (MEDI-N) MEDICAL & BIOLOGICAL LAB CO LTD.
PATENT INFO: WO 2000072011 A1 20001130 65p
APPLICATION INFO: WO 2000-JP3193 20000518
PRIORITY INFO: JP 1999-141187 19990521
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
OTHER SOURCE: 2001-032064 [04]
DESCRIPTION: Human **p53**-associated peptide fragment SEQ ID NO 8.

L9 ANSWER 21 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assaying phosphorylation enzyme activity on peptide immunologically with antibody to recognize phosphorylated state, useful in screening compounds to control enzyme activities e.g. signal transduction -
AN AAB45781 protein DGENE
AB This invention describes a novel **method** for assaying protein phosphorylation enzyme activity in a sample with DNA-dependent protein kinase, **ATM** or/and **ATR** as the enzyme for phosphorylation. The invention also describes (1) a **method** for screening inhibitors or promoters of the protein phosphorylation enzyme activity comprising: (a) incubation of the enzyme, substrate peptide and a test compound; (b) detecting the level of phosphorylation with an antibody; and (c) comparing the increase or decrease in phosphorylation with that of a control to select the compound; (2) a **method** for assaying dephosphorylation enzyme activity of a protein in a sample as for the phosphorylation **assay**; (3) a **method** for screening inhibitors or promoters of dephosphorylation enzyme activity of a protein carried out in a similar fashion as in (1); (4) an **assay** of DNA-dependent protein kinase activity comprising: (a) determination of the phosphorylation enzyme activity in the absence of a double-stranded DNA; (b) similar determination in presence of the DNA; and (c) comparing (a) and (b) to evaluate phosphorylation enzyme activity originated from the DNA-dependent protein kinase; (5) compounds that can regulate the protein phosphorylation enzyme activity thus screened by any of the methods; (6) an antibody that can recognize the phosphorylated state of a substrate peptide; and (7) an **assay** kit containing the antibody. The **assay** is useful for evaluating the ability of an enzyme to phosphorylate a peptide, which is useful in screening compounds to control enzyme activities e.g. signal transduction.

ACCESSION NUMBER: AAB45781 protein DGENE
TITLE: Assaying phosphorylation enzyme activity on peptide

immunologically with antibody to recognize phosphorylated state, useful in screening compounds to control enzyme activities e.g. signal transduction -
INVENTOR: Ogawa A; Kobayashi T; Yano M; Tamai K
PATENT ASSIGNEE: (MEDI-N)MEDICAL & BIOLOGICAL LAB CO LTD.
PATENT INFO: WO 2000072011 A1 20001130 65p
APPLICATION INFO: WO 2000-JP3193 20000518
PRIORITY INFO: JP 1999-141187 19990521
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
OTHER SOURCE: 2001-032064 [04]
DESCRIPTION: Human **p53**-associated peptide fragment SEQ ID NO 7.

L9 ANSWER 22 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assaying phosphorylation enzyme activity on peptide immunologically with antibody to recognize phosphorylated state, useful in screening compounds to control enzyme activities e.g. signal transduction -
AN AAB45780 protein DGENE
AB This invention describes a novel **method** for assaying protein phosphorylation enzyme activity in a sample with DNA-dependent protein kinase, **ATM** or/and **ATR** as the enzyme for phosphorylation. The invention also describes (1) a **method** for screening inhibitors or promoters of the protein phosphorylation enzyme activity comprising: (a) incubation of the enzyme, substrate peptide and a test compound; (b) detecting the level of phosphorylation with an antibody; and (c) comparing the increase or decrease in phosphorylation with that of a control to select the compound; (2) a **method** for assaying dephosphorylation enzyme activity of a protein in a sample as for the phosphorylation **assay**; (3) a **method** for screening inhibitors or promoters of dephosphorylation enzyme activity of a protein carried out in a similar fashion as in (1); (4) an **assay** of DNA-dependent protein kinase activity comprising: (a) determination of the phosphorylation enzyme activity in the absence of a double-stranded DNA; (b) similar determination in presence of the DNA; and (c) comparing (a) and (b) to evaluate phosphorylation enzyme activity originated from the DNA-dependent protein kinase; (5) compounds that can regulate the protein phosphorylation enzyme activity thus screened by any of the methods; (6) an antibody that can recognize the phosphorylated state of a substrate peptide; and (7) an **assay** kit containing the antibody. The **assay** is useful for evaluating the ability of an enzyme to phosphorylate a peptide, which is useful in screening compounds to control enzyme activities e.g. signal transduction.
ACCESSION NUMBER: AAB45780 protein DGENE
TITLE: Assaying phosphorylation enzyme activity on peptide immunologically with antibody to recognize phosphorylated state, useful in screening compounds to control enzyme activities e.g. signal transduction -
INVENTOR: Ogawa A; Kobayashi T; Yano M; Tamai K
PATENT ASSIGNEE: (MEDI-N)MEDICAL & BIOLOGICAL LAB CO LTD.
PATENT INFO: WO 2000072011 A1 20001130 65p
APPLICATION INFO: WO 2000-JP3193 20000518
PRIORITY INFO: JP 1999-141187 19990521
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
OTHER SOURCE: 2001-032064 [04]
DESCRIPTION: Human **p53**-associated peptide fragment SEQ ID NO 6.

L9 ANSWER 23 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assaying phosphorylation enzyme activity on peptide immunologically with antibody to recognize phosphorylated state, useful in screening compounds to control enzyme activities e.g. signal transduction -
AN AAB45779 protein DGENE
AB This invention describes a novel **method** for assaying protein phosphorylation enzyme activity in a sample with DNA-dependent protein

kinase, **ATM** or/and **ATR** as the enzyme for phosphorylation. The invention also describes (1) a **method** for screening inhibitors or promoters of the protein phosphorylation enzyme activity comprising: (a) incubation of the enzyme, substrate peptide and a test compound; (b) detecting the level of phosphorylation with an antibody; and (c) comparing the increase or decrease in phosphorylation with that of a control to select the compound; (2) a **method** for assaying dephosphorylation enzyme activity of a protein in a sample as for the phosphorylation **assay**; (3) a **method** for screening inhibitors or promoters of dephosphorylation enzyme activity of a protein carried out in a similar fashion as in (1); (4) an **assay** of DNA-dependent protein kinase activity comprising: (a) determination of the phosphorylation enzyme activity in the absence of a double-stranded DNA; (b) similar determination in presence of the DNA; and (c) comparing (a) and (b) to evaluate phosphorylation enzyme activity originated from the DNA-dependent protein kinase; (5) compounds that can regulate the protein phosphorylation enzyme activity thus screened by any of the methods; (6) an antibody that can recognize the phosphorylated state of a substrate peptide; and (7) an **assay** kit containing the antibody. The **assay** is useful for evaluating the ability of an enzyme to phosphorylate a peptide, which is useful in screening compounds to control enzyme activities e.g. signal transduction.

ACCESSION NUMBER: AAB45779 protein DGENE
TITLE: Assaying phosphorylation enzyme activity on peptide immunologically with antibody to recognize phosphorylated state, useful in screening compounds to control enzyme activities e.g. signal transduction -
INVENTOR: Ogawa A; Kobayashi T; Yano M; Tamai K
PATENT ASSIGNEE: (MEDI-N)MEDICAL & BIOLOGICAL LAB CO LTD.
PATENT INFO: WO 2000072011 A1 20001130 65p
APPLICATION INFO: WO 2000-JP3193 20000518
PRIORITY INFO: JP 1999-141187 19990521
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
OTHER SOURCE: 2001-032064 [04]
DESCRIPTION: Human **p53**-associated peptide fragment SEQ ID NO 5.

L9 ANSWER 24 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assaying phosphorylation enzyme activity on peptide immunologically with antibody to recognize phosphorylated state, useful in screening compounds to control enzyme activities e.g. signal transduction -
AN AAB45778 protein DGENE
AB This invention describes a novel **method** for assaying protein phosphorylation enzyme activity in a sample with DNA-dependent protein kinase, **ATM** or/and **ATR** as the enzyme for phosphorylation. The invention also describes (1) a **method** for screening inhibitors or promoters of the protein phosphorylation enzyme activity comprising: (a) incubation of the enzyme, substrate peptide and a test compound; (b) detecting the level of phosphorylation with an antibody; and (c) comparing the increase or decrease in phosphorylation with that of a control to select the compound; (2) a **method** for assaying dephosphorylation enzyme activity of a protein in a sample as for the phosphorylation **assay**; (3) a **method** for screening inhibitors or promoters of dephosphorylation enzyme activity of a protein carried out in a similar fashion as in (1); (4) an **assay** of DNA-dependent protein kinase activity comprising: (a) determination of the phosphorylation enzyme activity in the absence of a double-stranded DNA; (b) similar determination in presence of the DNA; and (c) comparing (a) and (b) to evaluate phosphorylation enzyme activity originated from the DNA-dependent protein kinase; (5) compounds that can regulate the protein phosphorylation enzyme activity thus screened by any of the methods; (6) an antibody that can recognize the phosphorylated state of a substrate peptide; and (7) an **assay** kit containing the antibody. The **assay** is useful for evaluating the ability of

an enzyme to phosphorylate a peptide, which is useful in screening compounds to control enzyme activities e.g. signal transduction.

ACCESSION NUMBER: AAB45778 protein DGENE
TITLE: Assaying phosphorylation enzyme activity on peptide immunologically with antibody to recognize phosphorylated state, useful in screening compounds to control enzyme activities e.g. signal transduction -
INVENTOR: Ogawa A; Kobayashi T; Yano M; Tamai K
PATENT ASSIGNEE: (MEDI-N) MEDICAL & BIOLOGICAL LAB CO LTD.
PATENT INFO: WO 2000072011 A1 20001130 65p
APPLICATION INFO: WO 2000-JP3193 20000518
PRIORITY INFO: JP 1999-141187 19990521
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
OTHER SOURCE: 2001-032064 [04]
DESCRIPTION: Human **p53**-associated peptide fragment SEQ ID NO 4.

Refine Search

Search Results -

Terms	Documents
L21 and ATR	0

Database:
US Pre-Grant Publication Full-Text Database
US Patents Full-Text Database
US OCR Full-Text Database
EPO Abstracts Database
JPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletins

Search: L23

Refine Search

Recall Text | Clear | Interrupt

Search History

DATE: Monday, April 19, 2004 Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT; PLUR=YES; OP=OR			
L23	l21 and ATR	0	L23
L22	L21 and ATM	0	L22
L21	CDS-1	20	L21
L20	HCDS-1	0	L20
L19	L18 and p53	2543	L19
L18	L17 and l16	105298	L18
L17	ATR and pathway inhibition	105350	L17
L16	ATM and pathway inhibition	106428	L16
L15	ATM adj2 inhibit	3	L15
L14	ATR adj2 inhibit	1	L14
L13	L12 and l10	764	L13
L12	L11 and p53	764	L12
L11	l9 and antagonist	17070	L11
L10	l8 and antagonist	17742	L10

h e b b cg b e e ch

L9	ATR agonist	23759	L9
L8	ATM agonist	62435	L8
L7	caffeine and ATM	225	L7
L6	caffeine and ATR	14	L6
L5	PCC and ATR	5	L5
L4	l1 and ATR	4	L4
L3	l1 and ATM	12	L3
L2	L1 and DNA-PK	5	L2
L1	wortmannin	132	L1

END OF SEARCH HISTORY

h e b b cg b e e ch

Hit List

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Search Results - Record(s) 1 through 10 of 14 returned.

☐ 1. Document ID: US 6593110 B2

L6: Entry 1 of 14 File: USPT Jul 15, 2003

US-PAT-NO: 6593110
DOCUMENT-IDENTIFIER: US 6593110 B2

TITLE: Checkpoint-activating oligonucleotides

DATE-ISSUED: July 15, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Guo; Zijian	San Diego	CA		
Dunphy; William G.	Altadena	CA		

US-CL-CURRENT: 435/69.1; 435/252.3, 435/320.1, 530/352, 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 2. Document ID: US 6565829 B2

L6: Entry 2 of 14 File: USPT May 20, 2003

US-PAT-NO: 6565829
DOCUMENT-IDENTIFIER: US 6565829 B2
**** See image for Certificate of Correction ****

TITLE: 5-arylsulfonyl indoles useful for treating disease

DATE-ISSUED: May 20, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Fu; Jian-Min	Kalamazoo	MI		

US-CL-CURRENT: 424/1.89; 424/1.11, 424/1.65, 424/1.81, 424/1.85, 424/9.1, 424/9.2, 424/9.3, 514/183, 514/410, 548/400, 548/414, 548/416

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

h e b b g e e e f e b ef b e

☐ 3. Document ID: US 6540978 B1

L6: Entry 3 of 14 File: USPT Apr 1, 2003

US-PAT-NO: 6540978
DOCUMENT-IDENTIFIER: US 6540978 B1

TITLE: Inhibitors of the bitter taste response

DATE-ISSUED: April 1, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Margolskee; Robert F.	Upper Montclair	NJ		
Ming; Ding	Whippany	NJ		

US-CL-CURRENT: 424/9.2; 424/1.11, 424/9.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 4. Document ID: US 6491933 B2

L6: Entry 4 of 14 File: USPT Dec 10, 2002

US-PAT-NO: 6491933
DOCUMENT-IDENTIFIER: US 6491933 B2

TITLE: Personal care articles comprising hotmelt compositions

DATE-ISSUED: December 10, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lorenzi; Marc Paul	Egham			GB
Smith, III; Edward Dewey	Mason	OH		
Phipps; Nicola Jacqueline	Bracknell			GB

US-CL-CURRENT: 424/401; 424/402, 424/404

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 5. Document ID: US 6428799 B1

L6: Entry 5 of 14 File: USPT Aug 6, 2002

US-PAT-NO: 6428799
DOCUMENT-IDENTIFIER: US 6428799 B1

TITLE: Personal care articles

h e b b g e e e f e b ef b e

DATE-ISSUED: August 6, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cen; Raymond Wei	Cincinnati	OH		
Phipps; Nichola Jacqueline	Warfield			GB
Smith, III; Edward Dewey	Mason	OH		

US-CL-CURRENT: 424/402; 424/400, 424/401

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

---

☐ 6. Document ID: US 6322801 B1

L6: Entry 6 of 14 File: USPT Nov 27, 2001

US-PAT-NO: 6322801
DOCUMENT-IDENTIFIER: US 6322801 B1

TITLE: Personal care articles

DATE-ISSUED: November 27, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lorenzi; Marc Paul	Egham			GB
Smith, III; Edward Dewey	Mason	OH		

US-CL-CURRENT: 424/402; 424/401, 424/443, 442/26, 510/131, 604/304

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

---

☐ 7. Document ID: US 6268140 B1

L6: Entry 7 of 14 File: USPT Jul 31, 2001

US-PAT-NO: 6268140
DOCUMENT-IDENTIFIER: US 6268140 B1
**** See image for Certificate of Correction ****

TITLE: Combinatorial metabolic libraries

DATE-ISSUED: July 31, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Stuart; W. Dorsey	San Francisco	CA		

US-CL-CURRENT: 435/6; 435/171, 435/254.11, 435/254.21, 435/254.3, 435/254.4, 435/254.5, 435/320.1, 435/440

h e b b g e e e f e b ef b e

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 8. Document ID: US 6267975 B1

L6: Entry 8 of 14 File: USPT Jul 31, 2001

US-PAT-NO: 6267975
DOCUMENT-IDENTIFIER: US 6267975 B1
**** See image for Certificate of Correction ****

TITLE: Personal care articles

DATE-ISSUED: July 31, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Smith, III; Edward Dewey	Mason	OH		
Lorenzi; Marc Paul	Egham			GB

US-CL-CURRENT: 424/401; 424/443

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 9. Document ID: US 6217889 B1

L6: Entry 9 of 14 File: USPT Apr 17, 2001

US-PAT-NO: 6217889
DOCUMENT-IDENTIFIER: US 6217889 B1
**** See image for Certificate of Correction ****

TITLE: Personal care articles

DATE-ISSUED: April 17, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lorenzi; Marc Paul	Egham			GB
Smith, III; Edward Dewey	Mason	OH		

US-CL-CURRENT: 424/401; 424/443

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 10. Document ID: US 5741665 A

L6: Entry 10 of 14 File: USPT Apr 21, 1998

h e b b g e e e f e b ef b e

US-PAT-NO: 5741665
DOCUMENT-IDENTIFIER: US 5741665 A

TITLE: Light-regulated promoters for production of heterologous proteins in filamentous fungi

DATE-ISSUED: April 21, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kato; Elie K.	Honolulu	HI		
Stuart; W. Dorsey	Kaneohe	HI		

US-CL-CURRENT: 435/69.1; 435/254.4, 536/24.1

h e b b g e e e f e b ef b e

Hit List

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Search Results - Record(s) 11 through 14 of 14 returned.

☐ 11. Document ID: US 5728675 A

L6: Entry 11 of 14 File: USPT Mar 17, 1998

US-PAT-NO: 5728675
DOCUMENT-IDENTIFIER: US 5728675 A
**** See image for Certificate of Correction ****

TITLE: Antemortem nutrient supplement for livestock

DATE-ISSUED: March 17, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Schaefer; Allan L.	Lacombe			CA
Jones; Stephen D. Morgan	Lacombe			CA
Stanley; Richard W.	Red Deer			CA
Turnbull; Ian K. S.	Lacombe			CA
Johanns; John R.	Grand Island	NE		

US-CL-CURRENT: 514/2; 514/23, 514/458, 514/474, 514/561

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 12. Document ID: US 5683899 A

L6: Entry 12 of 14 File: USPT Nov 4, 1997

US-PAT-NO: 5683899
DOCUMENT-IDENTIFIER: US 5683899 A

TITLE: Methods and compositions for combinatorial-based discovery of new multimeric molecules

DATE-ISSUED: November 4, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Stuart; W. Dorsey	Kaneche	HI		

US-CL-CURRENT: 435/69.6; 435/254.4, 435/454, 435/69.1

h e b b cg b cc e

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 13. Document ID: US 5643745 A

L6: Entry 13 of 14 File: USPT Jul 1, 1997

US-PAT-NO: 5643745
DOCUMENT-IDENTIFIER: US 5643745 A

TITLE: Heterologous dimeric proteins produced in heterokaryons

DATE-ISSUED: July 1, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Stuart; W. Dorsey	Kaneohe	HI		

US-CL-CURRENT: 435/69.1; 435/254.3, 435/69.4

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 14. Document ID: US 4496647 A

L6: Entry 14 of 14 File: USPT Jan 29, 1985

US-PAT-NO: 4496647
DOCUMENT-IDENTIFIER: US 4496647 A

TITLE: Treatment of image-forming laminated plate

DATE-ISSUED: January 29, 1985

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kawabe; Norio	Ohtsu			JP
Tsuda; Mikio	Ohmihachiman			JP
Kobashi; Sadao	Yohkaichi			JP

US-CL-CURRENT: 430/303; 430/166, 430/309

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Terms	Documents
caffeine and ATR	14

h e b b cg b cc e

Display Format: CIT Change Format

Previous Page Next Page Go to Doc#

h e b b cg b cc e

```
=> fil reg
FILE 'REGISTRY' ENTERED AT 13:05:14 ON 14 MAR 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   12 MAR 2004  HIGHEST RN 662722-88-5
DICTIONARY FILE UPDATES:  12 MAR 2004  HIGHEST RN 662722-88-5

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d ide can tot

L70  ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   182970-53-2  REGISTRY
CN   Kinase (phosphorylating), protein, Atm (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Ataxia telangiectasia-mutated protein kinase
CN   ATM kinase
CN   ATM protein kinase
CN   Gene ATM protein
CN   Gene ATM protein kinase
CN   Protein kinase Atm
MF   Unspecified
CI   MAN
SR   CA
LC   STN Files:   BIOSIS, CA, CAPLUS, TOXCENTER, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
             385 REFERENCES IN FILE CA (1907 TO DATE)
               1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             387 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE   1:  140:179247

REFERENCE   2:  140:175076

REFERENCE   3:  140:161467

REFERENCE   4:  140:161466

REFERENCE   5:  140:159713

REFERENCE   6:  140:143951

REFERENCE   7:  140:143679

REFERENCE   8:  140:143527

REFERENCE   9:  140:125875
```

REFERENCE 10: 140:124579

L70 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2004 ACS on STN
RN **182970-52-1** REGISTRY
CN Kinase (phosphorylating), protein, Atr (9CI) (CA INDEX NAME)
OTHER NAMES:
CN ATM- and Rad3-related protein kinase
CN Atr protein kinase
CN Checkpoint kinase
CN Checkpoint kinase ATR
CN DNA-dependent p53 kinase ATR
CN Protein kinase Atr
MF Unspecified
CI MAN
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, TOXCENTER, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
121 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
122 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:179154

REFERENCE 2: 140:176140

REFERENCE 3: 140:175076

REFERENCE 4: 140:159713

REFERENCE 5: 140:159510

REFERENCE 6: 140:126638

REFERENCE 7: 140:125875

REFERENCE 8: 140:75418

REFERENCE 9: 140:73208

REFERENCE 10: 140:72946

=> d his

(FILE 'HOME' ENTERED AT 12:37:50 ON 14 MAR 2004)
SET COST OFF

FILE 'HCAPLUS' ENTERED AT 12:38:07 ON 14 MAR 2004
L1 1 S WO98-GB2115/AP,PRN OR GB97-14971/AP,PRN
E LANE D/AU
E JACKSON S/AU
L2 131 S E3,E21
E JACKSON STEPHEN/AU
L3 13 S E3
L4 138 S E16,E17
L5 4 S E22
L6 3 S E23,E34
E LAKIN N/AU
L7 18 S E5,E7-E9,E11
E SMITH G/AU
L8 834 S E3,E12

```
L9            3 S E13
                E SMITH GRAEME/AU
L10          64 S E3,E6-E8
L11         374 S E27,E30
                E KUDOS/AP,CS
L12          15 S E4-E16
L13      527157 S ATM
L14        1767 S ATAX? TELANGIE?
L15        5842 S ATR
L16          83 S L2-L12 AND L13,L14
L17          10 S L2-L12 AND L15
L18          84 S L16,L17
L19          12 S L18 AND P53
                E P53/CT
                E E4+ALL
L20       15752 S E7-E10,E6+NT
L21          12 S L18 AND L20
L22          12 S L19,L21

     FILE 'REGISTRY' ENTERED AT 12:45:20 ON 14 MAR 2004
L23           1 S 182970-52-1

     FILE 'HCAPLUS' ENTERED AT 12:46:19 ON 14 MAR 2004
L24         122 S L23
L25         104 S (ATR OR CHECKPOINT)()PROTEIN KINASE
L26           2 S DNA DEPENDENT P53 KINASE ATR
L27          55 S PROTEIN KINASE ATR
L28           0 S ATR (1W) RAD3 RELATED PROTEIN KINASE
L29         251 S CHECKPOINT KINASE

     FILE 'REGISTRY' ENTERED AT 12:47:14 ON 14 MAR 2004
L30           1 S 182970-53-2

     FILE 'HCAPLUS' ENTERED AT 12:48:39 ON 14 MAR 2004
L31         387 S L30
L32         418 S ATM KINASE OR ATM PROTEIN KINASE OR PROTEIN KINASE ATM OR GEN
L33          20 S ATAX? TELANG? MUTAT? PROTEIN KINASE
L34          14 S L2-L12 AND L24-L29,L31-L33
L35          19 S L22,L34
L36          13 S L35 AND P53
L37           8 S L36 AND PHOSPHOR?
L38           5 S L36 NOT L37
                SEL DN AN 3
L39           4 S L38 NOT E1-E3
L40          12 S L37,L39
L41           6 S L35 NOT L36-L40
                SEL DN AN 2 5
L42           2 S L41 AND E4-E9
L43          14 S L40,L42 AND L1-L22,L24-L29,L31-L42
L44      533864 S L13-L15,L24-L29,L31-L33
L45         543 S L44 AND P53
L46         366 S L44 AND L20
L47         543 S L45,L46
L48         246 S L47 AND ?PHOSPHOR?
L49          19 S L48 AND SCREEN?
L50          70 S L47 AND (PD<=19970716 OR PRD<=19970716 OR AD<=19970716)
L51          12 S L50 AND L48
L52           2 S L50 AND SCREEN?
L53           7 S L50 AND ?ASSAY?
L54           2 S L50 AND (BIOCHEM?(L)METHOD?)/SC,SX
L55          18 S L51-L54
L56          17 S L55 NOT YTT?/TI
L57           2 S L43 AND (PD<=1997 OR PRD<=1997 OR AD<=1997)
```

```
L58          17 S L56,L57
L59          52 S L50 NOT L55-L58
                SEL DN AN 7 16 19 -22
                SEL DN AN 7 16 19-22
L60           6 S E76-E93
L61          23 S L58,L60 AND L1-L22,L24-L29,L31-L60
L62          17 S L61 AND ?RADIA?
L63          11 S L61 AND RADIA?/SC,SX
L64          18 S L62,L63
                SEL DN AN 3 13
L65           2 S E94-E99 AND L64
L66           5 S L61 NOT L64
L67           7 S L65,L66
L68          16 S L61-L66 NOT L67
                SEL HIT RN L61

     FILE 'REGISTRY' ENTERED AT 13:04:42 ON 14 MAR 2004
L69           1 S E100
L70           2 S L23,L30,L69

     FILE 'REGISTRY' ENTERED AT 13:05:14 ON 14 MAR 2004

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 13:05:20 ON 14 MAR 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1907 - 14 Mar 2004  VOL 140 ISS 12
FILE LAST UPDATED: 12 Mar 2004  (20040312/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> d l67 all tot

L67  ANSWER 1 OF 7  HCAPLUS  COPYRIGHT 2004 ACS on STN
AN   1999:81636  HCAPLUS
DN   130:150149
ED   Entered STN:  08 Feb 1999
TI   Ataxia-telangiectasia gene ATM protein has
     DNA-dependent protein kinase activity on p53 tumor antigen
IN   Lane, David Phillip; Hann, Byron; Jackson, Stephen Philip;
     Lakin, Nicholas David; Smith, Graeme Cameron Murray
PA   Cancer Research Campaign Technology Limited, UK
SO   PCT Int. Appl., 120 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
IC   ICM  G01N033-68
CC   6-3 (General Biochemistry)
```

Section cross-reference(s): 1, 7, **9**, **14**

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9904266	A2	19990128	WO 1998-GB2115	19980716 <--
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	GB 2327498	A1	19990127	GB 1998-15423	19980716 <--
	GB 2327498	B2	20020410		
	AU 9884492	A1	19990210	AU 1998-84492	19980716 <--
	AU 747594	B2	20020516		
	EP 996858	A2	20000503	EP 1998-935132	19980716 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2001510684	T2	20010807	JP 2000-503426	19980716 <--
	GB 2362952	A1	20011205	GB 2001-20368	19980716 <--
	GB 2362952	B2	20020306		
PRAI	GB 1997-14971	A	19970716 <--		
	GB 1998-15423	A3	19980716		
	WO 1998-GB2115	W	19980716 <--		

AB Interaction of the **ataxia-telangiectasia** gene-encoded **ATM** protein and related protein kinases such as **ATR** and DNA-activated protein kinase with **p53** is disclosed, in particular the **phosphorylation** of Ser-15 and Thr-18 by these proteins. The activity of the proteins increases in the presence of DNA. **Phosphorylation** of these sites of **p53** disrupts the interaction of **p53** with Mdm-2 which targets **p53** for degradation within the cell. **ATM** binds to DNA and possesses an associated protein kinase activity that is stimulated by DNA. These observations provide the basis for **assays** for modulators of **phosphorylation** dependent on the interaction between the proteins and **p53** or other proteins having similar **phosphorylation** sites. Methods of purifying **ATM** or **ATR** employing DNA or Ni2+-NTA are also disclosed.

ST **ataxia telangiectasia ATM protein kinase** DNA; **p53 phosphorylation ATM** protein **ataxia telangiectasia**; **screening** modulator **ATM** binding DNA kinase

IT **Proteins, specific or class**
RL: ARU (Analytical role, unclassified); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PUR (Purification or recovery); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(**ATM**; **ataxia-telangiectasia** gene
ATM protein has DNA-dependent protein kinase activity on **p53** tumor antigen)

IT **Proteins, specific or class**
RL: ARU (Analytical role, unclassified); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PUR (Purification or recovery); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(**ATR**; **ataxia-telangiectasia** gene
ATM protein has DNA-dependent protein kinase activity on **p53** tumor antigen)

IT Nervous system

(**ataxia telangiectasia**; **ataxia-telangiectasia** gene **ATM** protein has DNA-dependent protein kinase activity on **p53** tumor antigen)

IT DNA
RL: ARU (Analytical role, unclassified); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process)
(**ataxia-telangiectasia** gene **ATM** protein has DNA-dependent protein kinase activity on **p53** tumor antigen)

IT **p53 (protein)**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**ataxia-telangiectasia** gene **ATM** protein has DNA-dependent protein kinase activity on **p53** tumor antigen)

IT Mdm2 protein
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(disruption of **p53** binding; **ataxia-telangiectasia** gene **ATM** protein has DNA-dependent protein kinase activity on **p53** tumor antigen)

IT Drug **screening**
(for modulators of interaction; **ataxia-telangiectasia** gene **ATM** protein has DNA-dependent protein kinase activity on **p53** tumor antigen)

IT Protein motifs
(**phosphorylation** site; **ataxia-telangiectasia** gene **ATM** protein has DNA-dependent protein kinase activity on **p53** tumor antigen)

IT **Phosphorylation**, biological
(protein; **ataxia-telangiectasia** gene **ATM** protein has DNA-dependent protein kinase activity on **p53** tumor antigen)

IT 9026-43-1
RL: ARU (Analytical role, unclassified); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(DNA-dependent; **ataxia-telangiectasia** gene **ATM** protein has DNA-dependent protein kinase activity on **p53** tumor antigen)

IT 139-13-9D, Nitrilotriacetic acid, nickel complex 7440-02-0D, Nickel, nitrilotriacetic acid complex, uses
RL: NUU (Other use, unclassified); USES (Uses)
(matrix for affinity purification; **ataxia-telangiectasia** gene **ATM** protein has DNA-dependent protein kinase activity on **p53** tumor antigen)

L67 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1998:29790** HCAPLUS
DN **128:164103**
ED Entered STN: 19 Jan 1998
TI DNA damage induces **phosphorylation** of the amino terminus of **p53**
AU Siliciano, Janet D.; Canman, Christine E.; Taya, Yoichi; Sakaguchi, Kazuyasu; Appella, Ettore; Kastan, Michael B.
CS Oncology Center, Johns Hopkins School of Medicine, Baltimore, MD, 21205, USA
SO Genes & Development (**1997**), 11(24), 3471-3481
CODEN: GEDEEP; ISSN: 0890-9369
PB Cold Spring Harbor Laboratory Press
DT Journal
LA English

CC 6-3 (General Biochemistry)
Section cross-reference(s): 3

AB Data are presented demonstrating that DNA damage leads to specific post-translational modifications of **p53** protein. Using two-dimensional peptide mapping of in vivo radiolabeled **p53** tryptic phosphopeptides, recombinant truncated **p53** protein, and synthetic **p53** tryptic peptides, a unique **p53** phosphopeptide was identified after exposure of ML-1 cells to ionizing irradiation This peptide represents the first 24 amino acids of **p53** and contains three **phosphorylated** serine residues. A specific **p53** phosphopeptide antibody identified serine-15 as one of the two serines in **p53** that becomes **phosphorylated** following DNA damage induced by either ionizing irradiation (IR) or UV irradiation in multiple cell types. IR-induced **phosphorylation** of **p53** does not affect the kinetics of **p53** binding to or dissociating from DNA as assessed by electrophoretic mobility-shift **assays.** However, **p53 phosphorylation** induced by DNA damage correlates with enhanced transcription of downstream **p53** target genes. Low levels of phosphoserine-15 **p53** are detectable within 6 h after IR in AT cells, whereas lymphoblasts from normal individuals exhibit this modification within 1 h. In contrast, **phosphorylation** of **p53** on serine-15 is similar in normal and AT cells after UV irradiation Our results indicate that **p53** is **phosphorylated** in response to DNA damage, that this de novo **phosphorylation** may be involved in the subsequent induction and activation of **p53**, and that although **ATM** affects the kinetics of **p53 phosphorylation** after IR, it is not absolutely required for **phosphorylation** of **p53** on serine-15.

ST DNA damage protein **p53 phosphorylation**

IT **Proteins, specific or class**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**ATM**, effect on **p53 phosphorylation**; DNA damage induces **phosphorylation** of the amino terminus of **p53**)

IT IR **radiation**
UV **radiation**
(DNA damage by; DNA damage induces **phosphorylation** of the amino terminus of **p53**)

IT **p53 (protein)**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DNA damage induces **phosphorylation** of the amino terminus of **p53**)

IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(damage, DNA damage induces **phosphorylation** of the amino terminus of **p53**)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mdm-2, DNA damage effect on; DNA damage induces **phosphorylation** of the amino terminus of **p53**)

IT Cyclin dependent kinase inhibitors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(p21CIP1/WAF1, DNA damage effect on; DNA damage induces **phosphorylation** of the amino terminus of **p53**)

IT **Phosphorylation**, biological
(protein; DNA damage induces **phosphorylation** of the amino terminus of **p53**)

RE.CNT 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Adler, V; Proc Natl Acad Sci 1997, V94, P1686 HCAPLUS
(2) Baudier, J; Proc Natl Acad Sci 1992, V89, P11627 HCAPLUS
(3) Bischoff, J; Proc Natl Acad Sci 1990, V87, P4766 HCAPLUS
(4) Bogue, M; Genes & Dev 1996, V10, P553 HCAPLUS
(5) Boyle, W; Methods Enzymol 1991, V201, P110 HCAPLUS
(6) Canman, C; Cancer Res 1994, V54, P5054 HCAPLUS
(7) Canman, C; Genes & Dev 1995, V9, P600 HCAPLUS
(8) Chen, J; Mol Cell Biol 1993, V13, P4107 HCAPLUS
(9) Danska, J; Mol Cell Biol 1996, V16, P5507 HCAPLUS
(10) Derijard, B; Cell 1994, V76, P1025 HCAPLUS
(11) El-Deiry, W; Cell 1993, V75, P817 HCAPLUS
(12) Farmer, G; Mol Cell Biol 1996, V16, P4295 HCAPLUS
(13) Fiscella, M; Oncogene 1993, V8, P1519 HCAPLUS
(14) Gottlieb, T; Biochim Biophys Acta 1995, V1287, P77
(15) Graeber, T; Mol Cell Biol 1994, V14, P6264 HCAPLUS
(16) Guidos, C; Genes & Dev 1996, V10, P2038 HCAPLUS
(17) Hall, S; Nucleic Acids Res 1996, V24, P1119 HCAPLUS
(18) Hartwell, L; Science 1994, V266, P1821 HCAPLUS
(19) Haupt, Y; Nature 1997, V387, P296 HCAPLUS
(20) Huang, L; Cancer Res 1996, V56, P2940 HCAPLUS
(21) Hupp, T; Cell 1992, V71, P875 HCAPLUS
(22) Kastan, M; Cancer Res 1991, V51, P6304 HCAPLUS
(23) Kastan, M; Cell 1992, V71, P587 HCAPLUS
(24) Khanna, K; Oncogene 1993, V8, P3307 HCAPLUS
(25) King, D; Int J Peptide Protein Res 1990, V36, P255 HCAPLUS
(26) Kitagawa, M; EMBO J 1996, V15, P7060 HCAPLUS
(27) Ko, L; Genes & Dev 1996, V10, P1054 HCAPLUS
(28) Kubbutat, M; Nature 1997, V387, P299 HCAPLUS
(29) Lavin, M; Int J Radiat Biol 1994, V66, PS151 HCAPLUS
(30) Lees-Miller, S; Mol Cell Biol 1992, V12, P5041 HCAPLUS
(31) Linke, S; Genes & Dev 1996, V10, P934 HCAPLUS
(32) Lu, H; Mol Cell Biol 1997, V17, P5923 HCAPLUS
(33) Maki, C; Cancer Res 1996, V56, P2649 HCAPLUS
(34) Maltzman, W; Mol Cell Biol 1984, V4, P1689 HCAPLUS
(35) Mayr, G; Cancer Res 1995, V55, P2410 HCAPLUS
(36) Milne, D; J Biol Chem 1994, V269, P9253 HCAPLUS
(37) Milne, D; J Biol Chem 1995, V270, P5511 HCAPLUS
(38) Milne, D; Oncogene 1992, V7, P1361 HCAPLUS
(39) Momand, J; Cell 1992, V69, P1237 HCAPLUS
(40) Morgan, S; Adv Cancer Res 1997, V71, P1 HCAPLUS
(41) Nacht, M; Genes & Dev 1996, V10, P2055 HCAPLUS
(42) Nelson, W; Mol Cell Biol 1994, V14, P1815 HCAPLUS
(43) Picksley, S; Oncogene 1994, V9, P2523 HCAPLUS
(44) Rathmell, W; Cancer Res 1997, V57, P68 HCAPLUS
(45) Rosette, C; Science 1996, V274, P1194 HCAPLUS
(46) Santos, J; J Cell Sci 1996, V109, P1847 HCAPLUS
(47) Savitsky, K; Science 1995, V268, P1749 HCAPLUS
(48) Shieh, S; Cell 1997, V91, P325 HCAPLUS
(49) Shiloh, Y; J Clin Immunol 1996, V16, P254 HCAPLUS
(50) Takenaka, I; J Biol Chem 1995, V270, P5405 HCAPLUS
(51) Thut, C; Science 1995, V267, P100 HCAPLUS
(52) Wakamiya, T; Chem Lett 1994, P1099 HCAPLUS
(53) Wang, Y; Nature 1995, V376, P88 HCAPLUS
(54) Xu, Y; Genes & Dev 1996, V10, P2401 HCAPLUS
(55) Zakian, V; Cell 1995, V82, P685 HCAPLUS
(56) Zauberman, A; EMBO J 1993, V12, P2799 HCAPLUS

L67 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:738145 HCAPLUS
DN 128:57775
ED Entered STN: 24 Nov 1997

TI The old and the new in **p53** functional regulation
AU Magnelli, Lucia; Ruggiero, Marco; Chiarugi, Vincenzo
CS Laboratory of Molecular Biology at the Institute of General Pathology, University of Florence, Florence, 50134, Italy
SO Biochemical and Molecular Medicine (**1997**), 62(1), 3-10
CODEN: BMMEF4; ISSN: 1077-3150
PB Academic Press
DT Journal; General Review
LA English
CC 3-0 (Biochemical Genetics)
Section cross-reference(s): 13, 14
AB A review, with 76 refs. The gene termed **p53** is one of the most extensively studied for the past 18 yr and the amount of literature published on this gene reflects its relevance in the field of mol. oncol.; thus, loss or mutation of this oncosuppressor gene is probably the mol. lesion most frequently observed in human tumors. The aim of this minireview is to report, discuss, and interpret some recent observations on: (I) the relation with the **Ataxia-Telangiectasia** gene and with the signaling enzyme phosphatidylinositol 3-kinase; (II) the relationship between DNA damage, **p53**, and sensitivity to anticancer therapies; (III) the gain of function caused by mutations that transform the oncosuppressor **p53** gene into a dominant transforming oncogene and (IV) the **phosphorylative** regulation of **p53** and its relation with the mitogenic signaling cascade involving protein kinase C and tumor promoters.
ST review gene protein **p53**
IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(TP53; **p53** functional regulation)
IT Nervous system
(**ataxia telangiectasia**, gene; **p53** functional regulation in relation to **Ataxia-Telangiectasia** gene and with signaling enzyme phosphatidylinositol 3-kinase)
IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(damage, DNA damage and **p53** and sensitivity to anticancer therapies)
IT Transformation, neoplastic
(mutations that transform oncosuppressor **p53** gene into dominant transforming oncogene)
IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(oncogene; mutations that transform oncosuppressor **p53** gene into dominant transforming oncogene)
IT **p53 (protein)**
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**p53** functional regulation)
IT Signal transduction, biological
(**p53** functional regulation in relation to **Ataxia-Telangiectasia** gene and with signaling enzyme phosphatidylinositol 3-kinase)
IT Mitogens
Phosphorylation, biological
(**phosphorylative** regulation of **p53** and its relation with mitogenic signaling cascade involving protein kinase C and tumor promoter)
IT 115926-52-8, Phosphatidylinositol 3-kinase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**p53** functional regulation in relation to **Ataxia-Telangiectasia** gene and with signaling enzyme phosphatidylinositol 3-kinase)

IT 141436-78-4, Protein kinase C
RL: PRP (Properties)
(**phosphorylative** regulation of **p53** and its relationship with mitogenic signaling cascade involving protein kinase C and tumor promoter)

L67 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1997:387780** HCAPLUS
DN **127:63868**
ED Entered STN: 21 Jun 1997
TI **p53** and **ATM**: cell cycle, cell death, and cancer
AU Morgan, Susan E.; Kastan, Michael B.
CS The Johns Hopkins Oncology Center, Baltimore, MD, 21205, USA
SO Advances in Cancer Research (**1997**), 71, 1-25
CODEN: ACRSAJ; ISSN: 0065-230X
PB Academic
DT Journal; General Review
LA English
CC 14-0 (Mammalian Pathological Biochemistry)
AB A review with .apprx.200 refs. The development of a normal cell into a tumor cell appears to depend in part on mutations in genes that normally control cell cycle and cell death, thereby resulting in inappropriate cellular survival and tumorigenesis. **ATM** ("mutated in **ataxia-telangiectasia**") and **p53** are two gene products that are believed to play a major role in maintaining the integrity of the genome such that alterations in these gene products may contribute to increased incidence of genomic changes such as deletions, translocations, and amplifications, which are common during oncogenesis. **P53** is a critical participant in a signal transduction pathway that mediates either a G1 arrest or apoptosis in response to DNA damage. In addition, **p53** is believed to be involved in the mitotic spindle checkpoint and in the regulation of centrosome function. Following certain cytotoxic stresses, normal **ATM** function is required for **p53**-mediated G1 arrest. **ATM** is also involved in other cellular processes such as S phase and G2-M phase arrest and in radiosensitivity. The understanding of the roles that both **p53** and **ATM** play in cell cycle progression and cell death in response to DNA damage may provide new insights into the mol. mechanisms of cellular transformation and may help identify potential targets for improved cancer therapies.
ST review **p53** **ATM** cancer
IT Cell cycle
Cell death
Neoplasm
(**p53** and **ATM**: cell cycle, cell death, and cancer)
IT **p53 (protein)**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**p53** and **ATM**: cell cycle, cell death, and cancer)
IT 115926-52-8, Phosphatidylinositol 3-kinase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(gene **ATM**; **p53** and **ATM**: cell cycle, cell death, and cancer)
RE.CNT 190 THERE ARE 190 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Agamanolis, D; J Neuropathol Exp Neurol 1979, V38, P475 MEDLINE
(2) Al-Khodairy, F; EMBO J 1992, V11, P1343 HCAPLUS

(3) Al-Khodairy, F; Mol Biol Cell 1994, V5, P147 HCAPLUS
(4) Allen, J; Genes Dev 1994, V8, P2401 HCAPLUS
(5) Amromin, G; J Neuropathol Exp Neurol 1979, V38, P621 MEDLINE
(6) Anderson, C; Trends Biochem Sci 1993, V18, P433 HCAPLUS
(7) Arlett, C; Int J Radiat Biol 1983, V43, P157 MEDLINE
(8) Baker, B; Genetics 1978, V90, P531
(9) Baker, S; Science 1990, V249, P912 MEDLINE
(10) Banga, S; Mutat Res 1986, V163, P157 HCAPLUS
(11) Barak, Y; EMBO J 1993, V12, P461 HCAPLUS
(12) Bearnish, H; Radiat Res 1994, V138, PS130
(13) Biedermann, K; Proc Natl Acad Sci U S A 1991, V88, P1394 HCAPLUS
(14) Blunt, T; Cell 1995, V80, P813 HCAPLUS
(15) Brachman, D; Cancer Res 1992, V52, P4832 MEDLINE
(16) Brown, E; Nature (London) 1994, V369, P756 HCAPLUS
(17) Brugarolas, J; Nature (London) 1995, V377, P552 HCAPLUS
(18) Buckbinder, L; Nature (London) 1995, V377, P646 HCAPLUS
(19) Burgering, B; Nature (London) 1995, V376, P599 HCAPLUS
(20) Buttke, T; Immunol Today 1994, V15, P7 HCAPLUS
(21) Canman, C; Cancer Res 1994, V54, P5054 HCAPLUS
(22) Canman, C; Genes Dev 1995, V9, P600 HCAPLUS
(23) Carter, S; Cancer Res 1994, V54, P6270 HCAPLUS
(24) Chen, C; Proc Natl Acad Sci U S A 1994, V91, P2684 HCAPLUS
(25) Clarke, A; Nature (London) 1993, V362, P849 HCAPLUS
(26) Collins, M; J Exp Med 1992, V176, P1043 HCAPLUS
(27) Cox, R; Br J Cancer 1984, V46, P67
(28) Cross, S; Science 1995, V267, P1353 HCAPLUS
(29) Dameron, K; Science 1994, V265, P1582 HCAPLUS
(30) Debbas, M; Genes Dev 1993, V7, P546 HCAPLUS
(31) Degregori, J; Genes Dev 1995, V9, P2873 HCAPLUS
(32) Degregori, J; Mol Cell Biol 1995, V15, P4215 HCAPLUS
(33) Demers, G; Proc Natl Acad Sci U S A 1994, V91, P4382 HCAPLUS
(34) Deng, C; Cell 1995, V82, P675 HCAPLUS
(35) Dhand, R; EMBO J 1994, V13, P522 HCAPLUS
(36) Diller, L; Mol Cell Biol 1990, V10, P5772 HCAPLUS
(37) Donehower, L; Genes Dev 1995, V9, P882 HCAPLUS
(38) Donehower, L; Mol Carcinog 1995, V14, P16 HCAPLUS
(39) Donehower, L; Nature (London) 1992, V356, P215 HCAPLUS
(40) Downward, J; Nature (London) 1994, V371, P378 MEDLINE
(41) El-Deiry, W; Cell 1993, V75, P817 HCAPLUS
(42) Enoch, T; Trends Biochem Sci 1995, V20, P426 HCAPLUS
(43) Fan, S; Cancer Res 1995, V55, P1649 HCAPLUS
(44) Field, J; Eur J Cancer 1992, V28B, P67 MEDLINE
(45) Fisher, R; Cell 1994, V78, P713 HCAPLUS
(46) Flores-Rozas, H; Proc Natl Acad Sci U S A 1994, V91, P8655 HCAPLUS
(47) Ford, J; Proc Natl Acad Sci U S A 1995, V92, P8876 HCAPLUS
(48) Franke, T; Cell 1995, V81, P727 HCAPLUS
(49) Freund, G; Biochem Biophys Res Commun 1995, V206, P272 HCAPLUS
(50) Fujwara, T; Cancer Res 1994, V53, P4129
(51) Fukasawa, K; Science 1996, V271, P1744 HCAPLUS
(52) Gatti, R; Medicine 1991, V70, P99 MEDLINE
(53) Gottlieb, T; Cell 1993, V72, P131 HCAPLUS
(54) Graeber, T; Nature (London) 1996, V379, P88 HCAPLUS
(55) Grana, X; Oncogene 1995, V11, P211 HCAPLUS
(56) Greenwell, P; Cell 1995, V82, P823 HCAPLUS
(57) Hampton, G; Proc Natl Acad Sci U S A 1994, V91, P6953 HCAPLUS
(58) Han, J; Genes Dev 1996, V10, P461 HCAPLUS
(59) Hanks, S; Science 1988, V241, P42 HCAPLUS
(60) Hari, K; Cell 1995, V82, P815 HCAPLUS
(61) Harnden, D; Int J Radiat Biol 1994, V66, PS13 HCAPLUS
(62) Harper, J; Cell 1993, V75, P805 HCAPLUS
(63) Hartley, K; Cell 1995, V82, P849 HCAPLUS
(64) Hastie, H; Nature (London) 1990, V346, P866
(65) Hecht, F; Cancer Genet Cytogenet 1990, V46, P9 MEDLINE

(66) Heitman, J; Science 1991, V253, P905 HCAPLUS
(67) Helliwell, S; Mol Biol Cell 1994, V5, P105 HCAPLUS
(68) Hiles, I; Cell 1992, V70, P419 HCAPLUS
(69) Hollstein, M; Science 1991, V253, P49 HCAPLUS
(70) Hoyt, M; Cell 1991, V66, P507 HCAPLUS
(71) Huang, L; Proc Natl Acad Sci U S A 1996, V93, P4827 HCAPLUS
(72) Jamal, S; Oncogene 1995, V10, P2095 HCAPLUS
(73) Jimenez, G; Proc Nat Acad Sci U S A 1992, V89, P4952 HCAPLUS
(74) Johnson, D; Nature (London) 1993, V365, P349 HCAPLUS
(75) Jones, S; Nature (London) 1995, V378, P206 HCAPLUS
(76) Juven, T; Oncogene 1993, V8, P3411 HCAPLUS
(77) Kastan, M; Cancer Res 1991, V51, P6304 HCAPLUS
(78) Kastan, M; Cell 1992, V71, P587 HCAPLUS
(79) Kato, J; Mol Cell Biol 1994, V14, P2713 HCAPLUS
(80) Kato, R; Nucleic Acids Res 1994, V22, P3104 HCAPLUS
(81) Kazantsev, A; Science 1995, V270, P1003 HCAPLUS
(82) Keldysh, P; Genes Chromosomes Cancer 1993, V6, P45 HCAPLUS
(83) Kessis, T; Proc Natl Acad U S A 1993, V90, P3988 HCAPLUS
(84) Khanna, K; Oncogene 1993, V8, P3307 HCAPLUS
(85) Kobayashi, Y; J Immunol 1991, V147, P3201 HCAPLUS
(86) Kojis, T; Cancer Genet Cytogenet 1991, V56, P143 MEDLINE
(87) Kuerbitz, S; Proc Natl Acad Sci, U S A 1992, V89, P7491 HCAPLUS
(88) Kunz, J; Cell 1993, V73, P585 HCAPLUS
(89) Lees-Miller, S; Mol Cell Biol 1992, V12, P5041 HCAPLUS
(90) Levy, M; J Mol Biol 1992, V225, P951 HCAPLUS
(91) Levy, N; Mol Cell Biol 1993, V13, P7942 HCAPLUS
(92) Li, R; Cell 1991, V66, P519 HCAPLUS
(93) Li, R; Nature (London) 1994, V371, P534 HCAPLUS
(94) Lieber, M; Cell 1988, V55, P7 HCAPLUS
(95) Lin, Y; Mol Cell Biol 1995, V15, P6045 HCAPLUS
(96) Lipkowitz, S; J Exp Med 1990, V172, P409 HCAPLUS
(97) Little, J; Radiat Res 1985, V101, P81 MEDLINE
(98) Livingstone, L; Cell 1992, V70, P923 HCAPLUS
(99) Lotem, J; Blood 1993, V82, P1092 HCAPLUS
(100) Lowe, S; Genes Dev 1993, V7, P535 HCAPLUS
(101) Lowe, S; Nature (London) 1993, V362, P847 HCAPLUS
(102) Lowe, S; Proc Natl Acad Sci U S A 1994, V91, P2026 HCAPLUS
(103) Lustig, A; Proc Nat Acad Sci U S A 1986, V83, P1398 HCAPLUS
(104) Maltzman, W; Mol Cell Biol 1984, V4, P1689 HCAPLUS
(105) Martinez, J; Genes Dev 1991, V5, P151 HCAPLUS
(106) Matsushime, H; Cell 1992, V71, P323 HCAPLUS
(107) McKinnon, P; Hum Genet 1987, V75, P197 HCAPLUS
(108) Meek, D; Semin Cancer Biol 1994, V5, P203 HCAPLUS
(109) Meyn, M; Int J Radiat Biol 1994, V66, P141
(110) Meyn, M; Science 1993, V260, P1327 HCAPLUS
(111) Michalovitz, D; Cell 1990, V62, P671 HCAPLUS
(112) Milne, D; J Biol Chem 1994, V269, P9253 HCAPLUS
(113) Milne, D; J Biol Chem 1995, V270, P5511 HCAPLUS
(114) Miyashita, T; Oncogene 1994, V9, P1799 HCAPLUS
(115) Momand, J; Cell 1992, V69, P1237 HCAPLUS
(116) Montes de Oca Luna, R; Nature (London) 1995, V378, P203 MEDLINE
(117) Morrow, D; Cell 1995, V82, P831 HCAPLUS
(118) Nagasawa, H; Mutat Res 1985, V148, P71 MEDLINE
(119) Nelson, W; Mol Cell Biol 1994, V14, P1815 HCAPLUS
(120) Nevins, J; Curr Opin Gen Dev 1994, V4, P130 HCAPLUS
(121) Nevins, J; Science 1992, V258, P424 HCAPLUS
(122) Noda, A; Exp Cell Res 1994, V211, P90 HCAPLUS
(123) Okamota, K; EMBO J 1994, V13, P4816
(124) Oliner, J; Nature (London) 1992, V358, P80 HCAPLUS
(125) Oliner, J; Nature (London) 1993, V362, P857 HCAPLUS
(126) Oltvai, Z; Cell 1993, V74, P609 HCAPLUS
(127) Otto, A; Oncogene 1993, V8, P2591 HCAPLUS
(128) Painter, R; AT: Genetics, Neuropathology and Immunology of a Degenerative

Disease of Childhood 1985, P89 HCAPLUS
(129) Painter, R; Proc Natl Acad Sci U S A 1980, V77, P7315 HCAPLUS
(130) Pandita, T; Cytogenet Cell Genet 1995, V71, P86 HCAPLUS
(131) Papathanasiou, M; Mol Cell Biol 1991, V11, P1009 HCAPLUS
(132) Paterson, M; Nature (London) 1976, V260, P444 HCAPLUS
(133) Paules, R; Cancer Res 1995, V55, P1763 HCAPLUS
(134) Pejovic, T; Ann Med 1995, V27, P73 MEDLINE
(135) Perry, M; Proc Natl Acad Sci U S A 1993, V90, P11623 HCAPLUS
(136) Phipps, J; Adv Genet 1985, V23, P1 HCAPLUS
(137) Pines, J; Semin Cancer Biol 1995, V6, P63 HCAPLUS
(138) Powell, S; Cancer Res 1995, V55, P1643 HCAPLUS
(139) Ramqvist, T; Oncogene 1993, V8, P1495 HCAPLUS
(140) Rao, L; Proc Natl Acad Sci U S A 1992, V89, P7742 HCAPLUS
(141) Russell, K; Cancer Res 1995, V55, P1639 HCAPLUS
(142) Ryan, J; Mol Cell Biol 1993, V13, P711 HCAPLUS
(143) Sabatini, D; Cell 1994, V78, P35 HCAPLUS
(144) Sabers, C; J Biol Chem 1994, V270, P815
(145) Sachs, L; Apoptosis and the Immune System 1995, P371
(146) Sanchez, Y; Science 1996, V271, P357 HCAPLUS
(147) Savitsky, K; Hum Mol Genet 1995, V4, P2025 HCAPLUS
(148) Savitsky, K; Science 1995, V268, P1749 HCAPLUS
(149) Scheffner, M; Cell 1990, V63, P1129 HCAPLUS
(150) Seaton, B; Gene 1992, V119, P83 HCAPLUS
(151) Selvakumaran, M; Oncogene 1994, V9, P1791 HCAPLUS
(152) Shaw, P; Proc Natl Acad Sci U S A 1992, V89, P4495 HCAPLUS
(153) Sherr, C; Cell 1994, V79, P551 HCAPLUS
(154) Sherr, C; Genes Dev 1995, V9, P1149 HCAPLUS
(155) Shiloh, Y; Eur J Hum Genet 1995, V3, P116 HCAPLUS
(156) Shuefer, P; Cancer Res 1993, V53, P4946
(157) Slebos, R; Proc Natl Acad Sci U S A 1994, V91, P5320 HCAPLUS
(158) Slichenmeyer, W; Cancer Res 1993, V53, P4164
(159) Smith, M; Science 1994, V266, P1376 HCAPLUS
(160) Stan, R; J Biol Chem 1994, V269, P32027 HCAPLUS
(161) Sun, Z; Genes Dev 1996, V10, P395 HCAPLUS
(162) Swift, M; New Engl J Med 1987, V316, P1289 MEDLINE
(163) Swift, M; New Engl J Med 1991, V325, P1831 MEDLINE
(164) Symonds, H; Cell 1994, V78, P703 HCAPLUS
(165) Taccioli, G; Science 1994, V265, P1442 HCAPLUS
(166) Tanti, J; Biochem J 1994, V304, P17 HCAPLUS
(167) Tishler, R; Cancer Res 1993, V53, P2212 HCAPLUS
(168) Toker, A; J Biol Chem 1994, V269, P32358 HCAPLUS
(169) Tuteja, N; EMBO J 1994, V13, P4991 HCAPLUS
(170) Ullrich, S; J Biol Chem 1992, V267, P15259 HCAPLUS
(171) Vogelstein, B; Cell 1992, V70, P523 HCAPLUS
(172) Vorechovsky, I; Cancer Res 1996, V56, P2726 HCAPLUS
(173) Waga, S; Nature (London) 1994, V369, P574 HCAPLUS
(174) Wagner, A; Genes Dev 1994, V8, P2817 HCAPLUS
(175) Waldman, T; Cancer Res 1995, V55, P5187 HCAPLUS
(176) Wang, X; Nature Genet 1995, V10, P188 HCAPLUS
(177) Weinert, T; Genes Dev 1994, V8, P652 HCAPLUS
(178) Weinert, T; Radiat Res 1992, V132, P141 HCAPLUS
(179) White, E; Mol Cell Biol 1992, V12, P2570 HCAPLUS
(180) Wu, X; Genes Dev 1993, V7, P1126 HCAPLUS
(181) Xiong, Y; Genes Dev 1993, V7, P1572 HCAPLUS
(182) Xiong, Y; Nature (London) 1993, V366, P701 HCAPLUS
(183) Yao, K; J Natl Cancer Inst 1995, V87, P117 MEDLINE
(184) Yin, Y; Cell 1992, V70, P937 HCAPLUS
(185) Yonish-Rouach, E; Nature (London) 1991, V352, P345 HCAPLUS
(186) Zaki, S; Am J Pathol 1992, V140, P1345 MEDLINE
(187) Zambetti, G; FASEB J 1993, V7, P855 HCAPLUS
(188) Zauberman, A; Oncogene 1995, V10, P2361 HCAPLUS
(189) Zhan, Q; Cancer Res 1994, V54, P2755 HCAPLUS
(190) Zur Hausen, H; Advances in Viral Oncology 1989, P1

L67 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1997:272578** HCAPLUS
DN **126:313655**
ED Entered STN: 28 Apr 1997
TI Cell cycle checkpoint control
AU Murakami, Hiroshi; Okayama, Hiroto
CS Department of Biochemistry, Faculty of Medicine, The University of Tokyo, Japan
SO Experimental and Molecular Medicine (**1997**), 29(1), 1-11
CODEN: EMMEF3
PB Korean Society of Medical Biochemistry and Molecular Biology
DT Journal; General Review
LA English
CC 6-0 (General Biochemistry)
Section cross-reference(s): 14
AB A review, with 60 refs. Genetic instability is considered to be a major driving force of malignancy of cancer cells, and at least some of cancer-associated genetic instability is known to be caused by defects in the cell cycle checkpoint control. Patients of the cancer-prone genetic disorder **ataxia telangiectasia** frequently develop malignant lymphoma and their cells are defective in γ-irradiation responsive checkpoint control, whereas cells inactivated for the **p53** recessive oncoprotein are defective in DNA damage-induced checkpoint control and develop genetic instability. Cells contain two major cell cycle checkpoint control systems: DNA-replication checkpoint, DNA-damage checkpoint. These checkpoint systems are thought to consist of three functionally distinct components: sensors, checkpoint signal transducers and cell cycle effectors. Recent rapid progress in the identification of these components is beginning to prove this conceptual model and the generality of the checkpoint system among eukaryotes. The full understanding of the cell cycle checkpoint control system will provide deeper insights into the highly complex mechanisms of carcinogenesis and highlight possible targets for cancer therapy.
ST cell cycle checkpoint review
IT Cell cycle
(cell cycle checkpoint control)

L67 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:626474 HCAPLUS
DN 125:266633
ED Entered STN: 23 Oct 1996
TI Strange bedfellows in even stranger places: the role of **ATM** in meiotic cells, lymphocytes, tumors, and its functional links to **p53**
AU Hawley, R. Scott; Friend, Stephen H.
CS Dep. Genetics, Section Molecular, Cellular Biol., Univ. California, Davis, Davis, CA, 95616, USA
SO Genes & Development (**1996**), 10(19), 2383-2388
CODEN: GEDEEP; ISSN: 0890-9369
PB Cold Spring Harbor Laboratory Press
DT Journal; General Review
LA English
CC 3-0 (Biochemical Genetics)
AB A review with .apprx.48 refs. The value of the **ATM**-disruption mouse model as a critical tool for the study of human disease is discussed. Most critically, the mouse system provides a clear view of the function of **ATM** and **ATM**-like proteins in undamaged cells, such as meiotic cells and lymphocytes. In most cases, that role appears to still be centered on the processing of DNA breaks arising in various normal contexts. The mouse system also provides the best possible tool for **assaying** the role of **ATM** in the development of the nervous system, as a basis for understanding the neuropathol. of

ataxia telangiectasia. It is suggested that the **ATM**-like proteins exert their effects through coupling of meiotic and mitotic recombination events with the cell-cycle engine, control of chromosome compaction in meiotic cells, and direct effects of the replication and recombination process.

ST review **ATM** protein meiosis chromosome recombination

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**ATM**; role of **ATM** in meiotic cells, lymphocytes, tumors, and functional links to **p53**)

IT Lymphocyte
Meiosis
Recombination, genetic
(role of **ATM** in meiotic cells, lymphocytes, tumors, and functional links to **p53**)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TP53, role of **ATM** in meiotic cells, lymphocytes, tumors, and functional links to **p53**)

IT Nervous system
(disease, **ataxia telangiectasia**, role of **ATM** in meiotic cells, lymphocytes, tumors, and functional links to **p53**)

L67 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN

AN **1996:613792** HCAPLUS

DN **125:269322**

ED Entered STN: 16 Oct 1996

TI The role of **ataxia telangiectasia** and the DNA-dependent protein kinase in the **p53**-mediated cellular response to ionizing **radiation**

AU Jongmans, Wim; Artuso, Marina; Vuillaume, Michele; Bresil, Henriette; **Jackson, Stephen P.**; Hall, Janet

CS Unit Mech. Carcinogenesis, International Agency Res. Cancer, Lyon, 69372, Fr.

SO Oncogene (**1996**), 13(6), 1133-1138
CODEN: ONCNES; ISSN: 0950-9232

PB Stockton

DT Journal

LA English

CC 8-7 (**Radiation** Biochemistry)
Section cross-reference(s): 14

AB The DNA-dependent protein kinase (DNA-PK), whose catalytic subunit shows structural similarities to the **ataxia telangiectasis** (AT) gene product (**ATM**), has also been implicated in the **p53**-mediated signal transduction pathway that activates the cellular response to DNA damage produced by ionizing **radiation.** DNA-PK activity however was not found to be related to the transcriptional induction of WAF1/CIP1 (p21) in AT lymphoblastoid cell lines, following treatment with γ-rays. Normal protein and transcription levels of Ku70 and Ku80, as well as DNA-PK activity, were found in six different AT cell lines, 1-4 h following exposure to ionizing **radiation**, time-points where reduced and delayed transcriptional induction of WAF1/CIP1 (p21) was observed WAF1/CIP1 (p21) was found to be transcriptionally induced by **p53** in normal cell lines over this same time period following exposure to ionizing **radiation.** These results suggest that despite the findings that in vitro DNA-PK may **phosphorylate p53**, in vivo it would not appear to play a central role in the activation of **p53** as a transcription factor nor can it substitute for the **ATM** gene product in the cellular response following exposure to ionizing **radiation.**

ST ataxia protein kinase gamma ray; gene **p53** gamma ray protein kinase

IT Gamma ray
Translation, genetic
(**ataxia telangiectasia** and DNA-dependent protein kinase role in gene **p53**-mediated cellular response to γ-rays)
IT **Proteins, specific or class, biological studies**
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(ku70; **ataxia telangiectasia** and DNA-dependent protein kinase role in gene **p53**-mediated cellular response to γ-rays)
IT **Proteins, specific or class, biological studies**
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(ku80; **ataxia telangiectasia** and DNA-dependent protein kinase role in gene **p53**-mediated cellular response to γ-rays)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TP53, **ataxia telangiectasia** and DNA-dependent protein kinase role in gene **p53**-mediated cellular response to γ-rays)
IT Nervous system
(disease, **ataxia telangiectasia**, **ataxia telangiectasia** and DNA-dependent protein kinase role in gene **p53**-mediated cellular response to γ-rays)
IT **Proteins, specific or class, biological studies**
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(p21, **ataxia telangiectasia** and DNA-dependent protein kinase role in gene **p53**-mediated cellular response to γ-rays)
IT 9026-43-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(DNA-dependent; **ataxia telangiectasia** and DNA-dependent protein kinase role in gene **p53**-mediated cellular response to γ-rays)
IT 66-27-3, Methyl methanesulfonate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**ataxia telangiectasia** and DNA-dependent protein kinase role in gene **p53**-mediated cellular response to γ-rays of MMS)

=> d l68 all tot

L68 ANSWER 1 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:118589 HCAPLUS
DN 138:180694
ED Entered STN: 14 Feb 2003
TI Method to inhibit cell growth using oligonucleotides
IN Gilchrest, Barbara A.; Eller, Mark S.; Yaar, Mina
PA USA
SO U.S. Pat. Appl. Publ., 65 pp., Cont.-in-part of Appl. No. PCT/US01/10162.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K048-00
ICS C07H021-04
NCL 514044000; 536023200
CC 1-6 (Pharmacology)

Section cross-reference(s): **8**

FAN.CNT 6

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003032610	A1	20030213	US 2002-122630	20020412 <--
	WO 9639152	A1	19961212	WO 1996-US8386	19960603 <--
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA				
	US 6147056	A	20001114	US 1998-48927	19980326 <--
	WO 2001074342	A2	20011011	WO 2001-US10162	20010330
	WO 2001074342	A3	20020328		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	WO 2003087411	A1	20031023	WO 2003-US11393	20030411
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRAI	WO 1996-US8386	A2	19960603 <--		
	US 1998-48927	A2	19980326		
	US 2000-540843	A2	20000331		
	WO 2001-US10162	A2	20010330		
	US 1995-467012	A1	19950606 <--		
	US 1997-952697	A2	19971206		
	US 2002-122630	A	20020412		

AB Described are methods for treating hyperproliferative disorders, including cancers, by administering to the affected mammal (e.g., human) an effective amount of a composition comprising pTT or a composition comprising one or more oligonucleotides which share at least 50% nucleotide sequence identity with the human telomere overhang repeat. Methods of treatment or prevention of hyperproliferative diseases or pre-cancerous conditions affecting epithelial cells, such as psoriasis, atopic dermatitis, or hyperproliferative or UV-responsive dermatoses, hyperproliferative diseases of other epithelia and methods for reducing photoaging, or oxidative stress or for prophylaxis against or reduction in the likelihood of the development of skin cancer, are also disclosed.

ST cell proliferation inhibition oligonucleotide telomere overhang repeat

IT Skin, neoplasm
(Bowen's disease; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer)

IT Chemicals
Radiation
(DNA-damaging; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to

prevention of DNA damage)
IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(E2F1; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to role of **ATM** in **p53** and E2F1 induction)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ERCC3; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to gene expression)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GADD 45; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to gene expression)
IT Antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(MART-1; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to induction of differentiation and surface antigens)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Sdi I; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to gene expression)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TRP-1 (tyrosinase-related protein 1); method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to induction of differentiation and surface antigens)
IT Keratosis
(actinic; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to decreasing oxidative damage)
IT Drug delivery systems
(aerosols; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to formulation)
IT Skin, neoplasm
(basal cell carcinoma; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer)
IT Drug delivery systems
(carriers; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to formulation)
IT Uterus, neoplasm
(cervix; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer)
IT DNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(damage; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to prevention of DNA damage)
IT Skin, disease
(dyskeratosis; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to reversal of UV damage)
IT Glycoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gp100; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to induction of

differentiation and surface antigens)
IT Cell proliferation
(hyperproliferative disorder; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer)
IT Skin
(keratinocyte; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to decreasing keratinocyte proliferation)
IT Drug delivery systems
(liposomes; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to formulation)
IT Neoplasm
(metastasis; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer)
IT Melanoma
(metastatic; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer)
IT Antitumor agents
Carcinoma
Cytotoxic agents
Human
Leukemia
Lymphoma
Mammalia
Melanoma
Neoplasm
(method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer)
IT Oligonucleotides
Phosphorothioate oligodeoxyribonucleotides
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer)
IT **Phosphorylation**, biological
(method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to 5'-**phosphorylation**)
IT **p53 (protein)**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to activation of **p53** proteins)
IT Cell cycle
(method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to cell S-phase cycle arrest)
IT Antioxidants
Oxidative stress, biological
(method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to decreasing oxidative damage)
IT Mutation
(method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to effect on mutation frequency)
IT DNA repair
(method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to enhancement of repair of benzopyrene-induced DNA damage)
IT Immunomodulators
(method to inhibit cell growth using oligonucleotides to treat

hyperproliferative diseases such as cancer in relation to immunomodulator activity)

IT Apoptosis
(method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to induction of apoptosis)

IT Cell differentiation
(method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to induction of differentiation and surface antigens)

IT Epithelium
(method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to inhibiting epithelial cell proliferation)

IT Melanins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to melanogenesis)

IT Blister
Photoprotectants
Skin, neoplasm
UV **radiation**
(method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to reversal of UV damage)

IT Drug delivery systems
(oral; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to formulation)

IT Bone, neoplasm
(osteosarcoma; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer)

IT Telomeres (chromosome)
(overhang repeat, analogs; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer)

IT Cyclin dependent kinase inhibitors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p21CIP1; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to gene expression)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p73; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to role of p73 in apoptosis)

IT Keratosis
(seborrheic; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to decreasing oxidative damage)

IT Carcinoma
(squamous cell; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer)

IT Antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(surface, cancer cell differentiation-associated; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to induction of differentiation and surface antigens)

IT Skin, disease
(xeroderma pigmentosum; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to reversal of UV damage)

IT 61811-29-8, Apurinic endonuclease

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(1; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to apurinic endonuclease 1 induction)

IT 9054-89-1, Superoxide dismutase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(2; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to superoxide dismutase induction)

IT 57-55-6, Propylene glycol, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(formulation agent; method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to formulation)

IT 2642-45-7 89802-96-0 117490-04-7 123739-23-1D, analogs 244782-59-0 244782-60-3 497044-36-7 497044-37-8 497201-15-7 497201-16-8 497201-17-9 497201-18-0 497201-19-1
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer)

IT 9079-67-8, NADH dehydrogenase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to NADH dehydrogenase)

IT 9001-16-5, Cytochrome c oxidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to cytochrome c oxidase)

IT 50-32-8, Benzo[a]pyrene, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to enhancement of repair of benzopyrene-induced DNA damage)

IT 9002-10-2, Tyrosinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to induction of differentiation and surface antigens)

IT **182970-53-2, ATM protein kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to role of **ATM** in **p53** and E2F1 induction)

IT 120178-12-3, Telomerase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(method to inhibit cell growth using oligonucleotides to treat hyperproliferative diseases such as cancer in relation to telomerase)

IT 497894-82-3 497894-83-4 497894-84-5
RL: PRP (Properties)
(unclaimed nucleotide sequence; method to inhibit cell growth using oligonucleotides)

L68 ANSWER 2 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:7833 HCAPLUS
DN 130:47471
ED Entered STN: 06 Jan 1999
TI Methods for treating human cancers based on decreasing the level of **ATM** protein, and methods for identification of antitumor compounds
IN Westphal, Christoph H.; Leder, Philip
PA President and Fellows of Harvard College, USA

SO PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-70
ICS A61K039-395; A01N043-04; G01N033-574
CC 1-6 (Pharmacology)
Section cross-reference(s): **8**
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9856391	A1	19981217	WO 1998-US12217	19980611 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9880681	A1	19981230	AU 1998-80681	19980611 <--
PRAI US 1997-49593P	P	19970613 <--		
WO 1998-US12217	W	19980611		

AB Methods are provided for determining the appropriate therapy and/or prognosis for a cancer patient. A method for treating a neoplasm characterized by a decreased level of functional **P53** protein comprises (1) inducing a decreased level of biol. activity of an **ATM** protein to enhance the sensitivity of the neoplasm to **radiation**, and (2) exposing the neoplasm to **radiation.** The methodol. may use e.g. an anti-**ATM** neutralizing antibody or an antisense **ATM** nucleic acid. Also provided are methods for identifying compds. which will aid in the treatment of cancer.

ST **P53** cancer treatment **ATM** protein redn radiosensitization radiotherapy; antitumor agent **screening** **P53** cancer **ATM** protein redn

IT Nucleic acids
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**ATM** protein fragment- or mutant-encoding and antisense; cancer treatment based on decreasing **ATM** protein level, and methods for identification of antitumor compds.)

IT Mutation
(**ATM** protein; cancer treatment based on decreasing **ATM** protein level, and methods for identification of antitumor compds.)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**ATM**; cancer treatment based on decreasing **ATM** protein level, and methods for identification of antitumor compds.)

IT Lymphoma
(B-cell; tumor types associated with various **atm** and **p53** genotypes)

IT Lymphoma
(T-cell; tumor types associated with various **atm** and **p53** genotypes)

IT Antitumor agents
Antitumor agents
(bone marrow; cancer treatment based on decreasing **ATM** protein level, and methods for identification of antitumor compds.)

IT Antitumor agents
Apoptosis
Bone marrow

Digestive tract
Drug **screening**
Fibroblast
Hematopoietic precursor cell
Leukocyte
Platelet (blood)
Radiosensitizers, biological
Radiotherapy
Rodent
Spleen
(cancer treatment based on decreasing **ATM** protein level, and methods for identification of antitumor compds.)

IT **p53 (protein)**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cancer treatment based on decreasing **ATM** protein level, and methods for identification of antitumor compds.)

IT Hematopoietic precursor cell
(colony-forming; cancer treatment based on decreasing **ATM** protein level, and methods for identification of antitumor compds.)

IT Antitumor agents
Antitumor agents
(digestive tract; cancer treatment based on decreasing **ATM** protein level, and methods for identification of antitumor compds.)

IT Antitumor agents
Antitumor agents
(fibroblast neoplasm; cancer treatment based on decreasing **ATM** protein level, and methods for identification of antitumor compds.)

IT Sarcoma
(fibrosarcoma; cancer treatment based on decreasing **ATM** protein level, and methods for identification of antitumor compds.)

IT Immune system
(immunocompromised mammal; cancer treatment based on decreasing **ATM** protein level, and methods for identification of antitumor compds.)

IT Gamma ray
(irradiation; cancer treatment based on decreasing **ATM** protein level, and methods for identification of antitumor compds.)

IT Thymus gland
Thymus gland
(lymphoma; tumor types associated with various **atm** and **p53** genotypes)

IT Bone marrow
Bone marrow
Digestive tract
Digestive tract
Fibroblast
Fibroblast
(neoplasm, inhibitors; cancer treatment based on decreasing **ATM** protein level, and methods for identification of antitumor compds.)

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neutralizing, to **ATM** protein; cancer treatment based on decreasing **ATM** protein level, and methods for identification of antitumor compds.)

IT Neoplasm
(teratoma; tumor types associated with various **atm** and **p53** genotypes)

IT Genotypes
Lymphoma
Sarcoma

(tumor types associated with various **atm** and **p53** genotypes)

IT **182970-53-2, Protein kinase Atm**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cancer treatment based on decreasing **ATM** protein level, and methods for identification of antitumor compds.)

IT 50-02-2, Dexamethasone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(thymocyte apoptosis induced by γ-irradiation or; cancer treatment based on decreasing **ATM** protein level, and methods for identification of antitumor compds.)

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Enoch, T; Trends in Biochemical Science 1995, V20(10), P426 HCAPLUS
(2) Hawley, R; Genes & Development 1996, V10, P2383 HCAPLUS
(3) Jongmans, W; Oncogene 1996, V13, P1133 HCAPLUS
(4) Xie, G; Oncogene 1998, V16, P721 HCAPLUS
(5) Xu, Y; Genes & Development 1996, V10, P2401 HCAPLUS

L68 ANSWER 3 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1997:791805** HCAPLUS
DN **128:113561**
ED Entered STN: 19 Dec 1997
TI **Atm selectively regulates distinct p53-dependent cell-cycle checkpoint and apoptotic pathways**
AU Barlow, Carrolee; Brown, Kevin D.; Deng, Chu-Xia; Tagle, Danilo A.; Wynshaw-Boris, Anthony
CS Laboratory of Genetic Disease Research, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, 20892, USA
SO Nature Genetics (1997), 17(4), 453-456
CODEN: NGENEC; ISSN: 1061-4036
PB Nature America
DT Journal
LA English
CC 14-1 (Mammalian Pathological Biochemistry)
Section cross-reference(s): **8**, 13
AB **Atm** is part of a pathway that responds to DNA damage from ionizing **radiation** (IR). This pathway involves **p53**, as **Atm**-deficient cell lines and mice are defective in **p53** induction after IR.**p53** is a multi-functional protein that simultaneously regulates distinct downstream pathways controlling cell-cycle progression and apoptosis. However, the mechanisms by which **p53** differentially activates downstream pathways are unknown. To determine the relationship between **Atm** and **p53**, we examined cell-cycle and apoptotic responses in **Atm**-, **p53**- and p21-deficient mice after IR in the whole animal. As expected, **p53** protein levels were not induced by IR in thymus of **Atm**-deficient mice. IR-induced cell-cycle checkpoint function was also defective, and induction of p21 was attenuated in thymus from **Atm**-deficient mice. However, IR-induced apoptosis and Bax induction were completely normal; both of which are mediated by **p53.** IR-induced thymic apoptosis was suppressed in **Atm/p53** double-mutant mice but not in **Atm**/p21 double mutants, demonstrating **p53** dependence and **Atm** independence. Thus, **Atm** deficiency results in lack of **p53** induction by IR, but only selective disruption of **p53**-dependent functions. Our results support a model in which upstream effectors such as **Atm** selectively activate **p53** to regulate specific downstream pathways, providing a mechanism for controlling distinct cell-cycle and apoptotic responses.
ST **ATM** gene **p53** cell cycle apoptosis
IT Gene, animal

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**ATM**; **Atm** selectively regulates distinct **p53**-dependent cell-cycle checkpoint and apoptotic pathways)
IT Apoptosis
Cell cycle
Ionizing **radiation**
Signal transduction, biological
(**Atm** selectively regulates distinct **p53**-dependent cell-cycle checkpoint and apoptotic pathways)
IT **p53 (protein)**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**Atm** selectively regulates distinct **p53**-dependent cell-cycle checkpoint and apoptotic pathways)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TP53; **Atm** selectively regulates distinct **p53**-dependent cell-cycle checkpoint and apoptotic pathways)
IT Nervous system
(**ataxia telangiectasia**; **Atm** selectively regulates distinct **p53**-dependent cell-cycle checkpoint and apoptotic pathways)
IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(damage, **Atm** selectively regulates distinct **p53**-dependent cell-cycle checkpoint and apoptotic pathways)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p21; **Atm** selectively regulates distinct **p53**-dependent cell-cycle checkpoint and apoptotic pathways)
RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Barlow, C; Cell 1996, V86, P159 HCAPLUS
(2) Baskaran, R; Nature 1997, V387, P516 HCAPLUS
(3) Brown, K; Proc Natl Acad Sci USA 1997, V94, P1840 HCAPLUS
(4) Brugarolas, J; Nature 1995, V377, P552 HCAPLUS
(5) Chen, G; J Biol Chem 1996, V271, P33693 HCAPLUS
(6) Chen, X; Genes Dev 1996, V10, P2438 HCAPLUS
(7) Clarke, A; Nature 1993, V362, P849 HCAPLUS
(8) Deng, C; Cell 1995, V82, P675 HCAPLUS
(9) El-Deiry, W; Cell 1993, V75, P817 HCAPLUS
(10) Friedlander, P; Mol Cell Biol 1996, V16, P4961 HCAPLUS
(11) Harlow, E; Antibodies:A Laboratory Manual 1988
(12) Harper, J; Cell 1993, V75, P805 HCAPLUS
(13) Jacks, T; Curr Biol 1994, V4, P1 HCAPLUS
(14) Kastan, M; Cancer Res 1991, V51, P6304 HCAPLUS
(15) Kastan, M; Cell 1992, V71, P587 HCAPLUS
(16) Khanna, K; Oncogene 1993, V8, P3307 HCAPLUS
(17) Ko, L; Genes Dev 1996, V10, P1054 HCAPLUS
(18) Lakin, N; Oncogene 1996, V13, P2707 HCAPLUS
(19) Levine, A; Cell 1997, V88, P323 HCAPLUS
(20) Lowe, S; Nature 1993, V362, P847 HCAPLUS
(21) Lu, X; Cell 1993, V75, P765 HCAPLUS
(22) Luna, L; Histopathological Methods and Color Atlas of Special Stains and Tissue 1992
(23) Meyn, M; Cancer Res 1995, V55, P5991 HCAPLUS
(24) Meyn, M; Int J Radiat Biol 1994, V66, PS141 HCAPLUS
(25) Miyashita, T; Cell 1995, V80, P293 HCAPLUS
(26) Pietenpol, J; Proc Natl Acad Sci USA 1994, V91, P1998 HCAPLUS
(27) Santana, P; Cell 1996, V86, P189 HCAPLUS
(28) Shiloh, Y; Eur J Hum Genet 1995, V3, P116 HCAPLUS
(29) Westphal, C; Nature Genet 1997, V16, P397 HCAPLUS
(30) White, R; Cytometry 1990, V11, P314 MEDLINE

(31) Xu, Y; Genes Dev 1996, V10, P2401 HCAPLUS

L68 ANSWER 4 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:603966 HCAPLUS
DN 127:244866
ED Entered STN: 24 Sep 1997
TI Elevated frequency of **p53**-independent apoptosis after **irradiation** increases levels of DNA breaks in **ataxia telangiectasia** lymphoblasts
AU Humar, B.; Muller, H.; Scott, R. J.
CS Human Genetics, Department of Research, University Hospital, Basel, CH-4031, Switz.
SO International Journal of Radiation Biology (**1997**), 72(3), 257-269
CODEN: IJRBE7; ISSN: 0955-3002
PB Taylor & Francis
DT Journal
LA English
CC 8-7 (**Radiation** Biochemistry)
Section cross-reference(s): 14
AB **Ataxia telangiectasia** is a recessive genetic disease featuring cerebellar degeneration, developmental abnormalities, high cancer risk, immunodeficiency, and radiosensitivity. Increased levels of unrepaired DNA breaks have been observed in **irradiated ataxia telangiectasia** cells compared to normal cells but no specific DNA break rejoining rate deficiency has been defined. Alterations in **radiation**-induced **p53**-dependent apoptosis have been reported for **ataxia telangiectasia** cells. This study investigated the **radiation** response of **ataxia telangiectasia** lymphoblastoid cells using the comet **assay** and uncovered a new feature of this technique, namely its capacity to preferentially detect living cells. After exposure to γ-rays, **ataxia telangiectasia** lymphoblasts exhibit an elevated frequency of cells committed to die via apoptosis. The observed apoptosis, which is likely to be independent of **p53**, leads to a higher number of DNA breaks during the first 3 h post irradiation in **ataxia telangiectasia** cells, relative to controls. Apart from cells undergoing apoptosis, **ataxia telangiectasia** lymphoblasts have an identical capacity to rejoin **radiation**-induced DNA breaks as controls. Results suggest that **p53**-independent apoptosis may contribute to the radiosensitivity and the immune defects of **ataxia telangiectasia** patients.
ST gamma ray apoptosis DNA break ataxia
IT Nervous system
(**ataxia telangiectasia**; γ-ray-induced elevated frequency of **p53**-independent apoptosis increasing DNA breaks in **ataxia telangiectasia** lymphoblasts)
IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(damage; γ-ray-induced elevated frequency of **p53**-independent apoptosis increasing DNA breaks in **ataxia telangiectasia** lymphoblasts)
IT Apoptosis
Gamma ray
Lymphoblast
(γ-ray-induced elevated frequency of **p53**-independent apoptosis increasing DNA breaks in **ataxia telangiectasia** lymphoblasts)

L68 ANSWER 5 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1997:464505** HCAPLUS

DN **127:118651**
ED Entered STN: 24 Jul 1997
TI Induction of the **p53** response
AU Yamaizumi, Masaru
CS Sch. Med., Kumamoto Univ., Kumamoto, 862, Japan
SO Tanpakushitsu Kakusan Koso (**1997**), 42(10), 1576-1584
CODEN: TAKKAJ; ISSN: 0039-9450
PB Kyoritsu
DT Journal; General Review
LA Japanese
CC 6-0 (General Biochemistry)
Section cross-reference(s): **8**, 14
AB A review, with 17 refs., on induction of **p53** protein by x-ray or UV-induced DNA damage and diseases with DNA repair deficiency, **p53** induction upon cellular stress, e.g. heat shock, osmotic shock, etc., and mechanism of these **p53** responses. Some antitumor agents also induce **p53** in cells at the S-phase. It is not known what the sensor for **p53** responses is. **ATM** (the gene mutated in **ataxia-telangiectasia**) and BLM (the gene mutated in Bloom's syndrome) may be involved in ionizing **radiation**-induced and UV-induced **p53** responses, resp. PKC is a potent mediator in the pathways of both responses. Tumor-suppressive activity of **p53** requires its nuclear localization. **P53** response in viral infection and downregulation of **p53** by mdm2 gene product are also discussed.
ST review **p53** response **radiation** stress; signal transduction **p53** induction review
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(TP53; mechanism of **p53** response upon **radiation**-induced DNA damage and antitumor agents and heat shock)
IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(damage; mechanism of **p53** response upon **radiation**-induced DNA damage and antitumor agents and heat shock)
IT **Radiation**
Signal transduction, biological
Stress, animal
(mechanism of **p53** response upon **radiation**-induced DNA damage and antitumor agents and heat shock)
IT **p53 (protein)**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mechanism of **p53** response upon **radiation**-induced DNA damage and antitumor agents and heat shock)

L68 ANSWER 6 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:349207 HCAPLUS
DN 126:340510
ED Entered STN: 04 Jun 1997
TI Cellular radiosensitivity, radioresistant DNA synthesis, and defect in radioinduction of **p53** in fibroblasts from atherosclerosis patients
AU Nasrin, Nargis; Mimish, Layth A.; Manogaran, Pulicat S.; Kunhi, Mohammed; Sigut, David; Al-Sedairy, Sultan; Hannan, Mohammed A.
CS Department of Biological and Medical Research, King Faisal Specialist Hospital and Research Centre, Riyadh, 11211, Saudi Arabia
SO Arteriosclerosis, Thrombosis, and Vascular Biology (**1997**), 17(5), 947-953
CODEN: ATVBFA; ISSN: 1079-5642
PB American Heart Association

DT Journal
LA English
CC 8-7 (**Radiation** Biochemistry)
Section cross-reference(s): 14
AB Earlier studies have suggested that both cancer and atherosclerosis may follow a common pathway in the early stage of development and share certain risk factors. One report indicated that the gene responsible for the radiosensitive, cancer-prone, multisystem disorder **ataxia telangiectasia** (AT) may increase the risk of developing ischemic heart disease. The present studies were carried out to find similarities, if any, between atherosclerosis patients and AT homozygotes or heterozygotes (ATHs) in their cellular/mol. response to ionizing **radiation**, which acts as a carcinogen as well as an atherogen. Fibroblast cell strains developed from healthy subjects and from AT homozygotes, ATHs, and atherosclerosis patients were compared for (1) survival, by the colony-forming **assay** and (2) DNA synthesis inhibition after irradiation, determined by [3H]thymidine incorporation, cell cycle distribution, and the expression of **p53** and p21 proteins, analyzed by flow cytometry. Fibroblasts from the atherosclerosis patients as a group, compared with the healthy subjects, showed enhanced sensitivity to chronic (low-dose-rate) irradiation A majority of the cell strains representing atherosclerosis patients exhibited varying degrees of radioresistant DNA synthesis (RDS), with roughly 33% showing an AT-like and the rest an ATH-like response. All cell strains with an AT-like and one quarter with an ATH-like RDS were found to be defective in the radioinduction of both **p53** and p21 proteins, which are concerned with cell cycle regulation. An absence of G1 arrest after irradiation was observed in cell strains lacking a radioinduced expression of **p53** and p21. Cellular/mol. defects leading to increased radiosensitivity, reduced induction of **p53**/p21, and cell cycle deregulation found to be associated with cancer-prone disorders such as AT may constitute important risk factors for atherosclerosis as well.
ST gamma ray fibroblast atherosclerosis; DNA formation atherosclerosis gamma ray; **p53** induction gamma ray
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(TP53; cellular radiosensitivity, radioresistant DNA synthesis, and defect in **p53** radioinduction in γ- **irradiated** fibroblasts from atherosclerosis patients)
IT Atherosclerosis
DNA formation
Gamma ray
(cellular radiosensitivity, radioresistant DNA synthesis, and defect in **p53** radioinduction in γ- **irradiated** fibroblasts from atherosclerosis patients)

L68 ANSWER 7 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1997:314112** HCAPLUS
DN **127:15755**
ED Entered STN: 16 May 1997
TI Cellular localization of the **ataxia-telangiectasia** (**ATM**) gene product and discrimination between mutated and normal forms
AU Watters, Dianne; Khanna, Kum Kum; Beamish, Heather; Birrell, Geoffrey; Spring, Kevin; Kedar, Padmini; Gatei, Magtouf; Stenzel, Deborah; Hobson, Karen; et al.
CS The Queensland Cancer Fund Research Unit, Queensland Institute of Medical Research, P.O. Royal Brisbane Hospital, Brisbane, 4029, Australia
SO Oncogene (**1997**), 14(16), 1911-1921
CODEN: ONCNES; ISSN: 0950-9232
PB Stockton

DT Journal
LA English
CC 13-1 (Mammalian Biochemistry)
AB The recently cloned gene (**ATM**) mutated in the human genetic disorder **ataxia-telangiectasia** (A-T) is involved in DNA damage response at different cell cycle checkpoints and also appears to have a wider role in signal transduction. Antibodies prepared against peptides from the predicted protein sequence detected a .apprx.350-kDa protein corresponding to the open reading frame, which was absent in 13/23 A-T homozygotes. Subcellular fractionation, immunoelectronmicroscopy, and immunofluorescence showed that the **ATM** protein is present in the nucleus and cytoplasmic vesicles. This distribution did not change after irradiation Evidence is also provided that **ATM** protein binds to **p53** and this association is defective in A-T cells compatible with the defective **p53** response in these cells. These results provide further support for a role for the **ATM** protein as a sensor of DNA damage and in a more general role in cell signaling, compatible with the broader phenotype of the syndrome.
ST **ATM** gene protein cell localization; **p53 ATM** gene protein **ataxia telangiectasia**
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**ATM**; cellular localization of **ataxia-telangiectasia** (**ATM**) gene product and its binding to **p53** is defective in human A-T cells)
IT Nervous system
(**ataxia telangiectasia**; cellular localization of **ataxia-telangiectasia** (**ATM**) gene product and its binding to **p53** is defective in human A-T cells)
IT Cell nucleus
Cytoplasm
Radiation
Signal transduction, biological
(cellular localization of **ataxia-telangiectasia** (**ATM**) gene product and its binding to **p53** is defective in human A-T cells)
IT **p53 (protein)**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cellular localization of **ataxia-telangiectasia** (**ATM**) gene product and its binding to **p53** is defective in human A-T cells)
IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(damage; cellular localization of **ataxia-telangiectasia** (**ATM**) gene product and its binding to **p53** is defective in human A-T cells)
IT **Proteins, specific or class**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(gene **ATM**; cellular localization of **ataxia-telangiectasia** (**ATM**) gene product and its binding to **p53** is defective in human A-T cells)
RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Al-Khodairy, F; Mol Biol Cell 1994, P147 HCAPLUS
(2) Barlow, C; Cell 1996, V86, P159 HCAPLUS
(3) Beamish, H; Int J Radiat Biol 1994, V65, P175 MEDLINE
(4) Beamish, H; J Biol Chem 1996, V271, P486
(5) Beamish, H; Oncogene 1996, V13, P963 HCAPLUS
(6) Brown, E; Nature 1994, V369, P756 HCAPLUS
(7) Brown, E; Nature 1995, V377, P441 HCAPLUS

(8) Canman, C; Cancer Res 1994, V54, P5054 HCAPLUS
(9) Carpenter, C; Mol Cell Biol 1993, V13, P1657 HCAPLUS
(10) Chen, Y; Science 1995, V270, P789 HCAPLUS
(11) Dhand, R; EMBO J 1994, V13, P522 HCAPLUS
(12) Finnie, N; Phil Trans R Soc Lond B 1996, V351, P173 HCAPLUS
(13) Ford, M; Mutation Res 1984, V125, P115 MEDLINE
(14) Gatti, R; Nature 1988, V336, P577 MEDLINE
(15) Hari, K; Cell 1995, V82, P815 HCAPLUS
(16) Harlow, E; Antibodies:a laboratory manual 1988
(17) Harnden, D; Int J Radiat Biol 1994, V66, PS13 HCAPLUS
(18) Hartley, K; Cell 1995, V82, P849 HCAPLUS
(19) Houldsworth, J; Nucleic Acids Res 1980, V8, P3709 HCAPLUS
(20) Hunter, T; Cell 1995, V83, P1 HCAPLUS
(21) Imray, F; Mutation Res 1983, V112, P369 MEDLINE
(22) Jackson, S; Curr Biol 1995, V5, P1210 HCAPLUS
(23) Jimenez, G; Proc Natl Acad Sci USA 1992, V89, P4952 HCAPLUS
(24) Jung, M; Science 1995, V268, P1619 HCAPLUS
(25) Kastan, M; Cell 1992, V71, P587 HCAPLUS
(26) Khanna, K; Oncogene 1993, V8, P3307 HCAPLUS
(27) Khanna, K; Oncogene 1995, V11, P609 HCAPLUS
(28) Kondo, N; Scand J Immunol 1993, V38, P45 MEDLINE
(29) Kunz, J; Cell 1993, V73, P585 HCAPLUS
(30) Lavin, M; Ann Rev Immunol in press 1997
(31) Lavin, M; Int J Radiat Biol 1994, V66, PS151 HCAPLUS
(32) Lavin, M; Trends Biochem Sci 1995, V20, P382 MEDLINE
(33) Lu, X; Cell 1993, V75, P765 HCAPLUS
(34) Maldonado, E; Nature 1996, V381, P86 HCAPLUS
(35) Meyn, M; Cancer Res 1995, V55, P5591
(36) Morrow, D; Cell 1995, V82, P831 HCAPLUS
(37) Nacht, M; Genes and Dev 1996, V10, P2055 HCAPLUS
(38) Nagasawa, H; Mutation Res 1983, V109, P297 MEDLINE
(39) O'Connor, R; Clin Immun Immunopathol 1980, V15, P66 MEDLINE
(40) Painter, R; Proc Natl Acad Sci USA 1980, V77, P7315 HCAPLUS
(41) Paules, R; Cancer Res 1995, V55, P1763 HCAPLUS
(42) Paulovich, A; Cell 1995, V82, P841 HCAPLUS
(43) Roest, P; Hum Mol Genet 1993, V2, P1719 HCAPLUS
(44) Rotman, G; J Clin Immunol 1996, V16, P254
(45) Rudolph, N; Mutation Res 1989, V211, P19 MEDLINE
(46) Sabatini, D; Cell 1994, V78, P35 HCAPLUS
(47) Savitsky, K; Hum Mol Genet 1995, V4, P2025 HCAPLUS
(48) Savitsky, K; Science 1995, V268, P1749 HCAPLUS
(49) Schnitt, S; Science 1996, V272, P123
(50) Scott, D; Int J Radiat Biol 1982, V42, P679 MEDLINE
(51) Sedgwick, R; Hereditary Neuropathies and Spinocerebellar Atrophies 1991, P347
(52) Shafman, T; Cancer Res 1995, V55, P3242 HCAPLUS
(53) Shiloh, Y; Eur J Hum Genet 1995, V3, P116 HCAPLUS
(54) Siddo-Atwal, C; Cancer Res 1996, V56, P443
(55) Singh, S; Mol Cell Biol 1990, V10, P5279 HCAPLUS
(56) Stolzenbach, F; Methods in Enzymol 1966, V9, P278 HCAPLUS
(57) Teale, B; J Biol Chem 1992, V267, P10295 HCAPLUS
(58) Teale, B; J Biol Chem 1993, V268, P22450 HCAPLUS
(59) Telatar, M; Am J Hum Genet 1996, V59, P40 HCAPLUS
(60) Tokuyasu, K; Histochemical J 1989, V21, P163 MEDLINE
(61) Uziel, T; Genomics 1996, V33, P317 HCAPLUS
(62) Xu, Y; Genes and Dev 1996, V10, P2389
(63) Xu, Y; Genes and Dev 1996, V10, P2411 HCAPLUS
(64) Zakian, V; Cell 1995, V82, P1

L68 ANSWER 8 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1997:313626** HCAPLUS
DN **127:32021**
ED Entered STN: 16 May 1997

TI Genetic interactions between **atm** and **p53** influence cellular proliferation and **irradiation**-induced cell cycle checkpoints
AU Westphal, Christoph Heiner; Schmaltz, Cornelius; Rowan, Sheldon; Elson, Ari; Fisher, David Erich; Leder, Philip
CS Department of Genetics and Howard Hughes Medical Institute, Harvard Medical School, The Weizmann Institute of Science, Boston, MA, 02115, USA
SO Cancer Research (**1997**), 57(9), 1664-1667
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
CC 13-6 (Mammalian Biochemistry)
Section cross-reference(s): 3
AB **Ataxia-telangiectasia** and Li-Fraumeni syndrome, pleiotropic disorders caused by mutations in the genes **atm** and **p53**, share a marked increase in cancer rates. A number of studies have argued for an interaction between these two genes. Specifically, **atm** is placed upstream of **p53** in mediating G1-S cell cycle checkpoint control, and both **atm** and **p53** are believed to influence cellular proliferation. To analyze the genetic interactions of **atm** and **p53**, mouse embryonic fibroblasts (MEFs) homozygously deficient for both **atm** and **p53** were used to assess cell cycle and growth control. These double-null fibroblasts proliferate rapidly and fail to exhibit the premature growth arrest seen with **atm**-null MEFs. MEFs null for both **atm** and **p53** do not express any p21cipl/wafl, showing that **p53** is required for p21cipl/waft expression in an **atm**-null background. By contrast, homozygous loss of either **atm**, **p53**, or both results in similar abnormalities of the irradiation-induced G1-S cell cycle checkpoint. The authors' results suggest two sep. pathways of interaction between **atm** and **p53**, one linear, involving G1-S cell cycle control, and another more complex, involving aspects of growth regulation.
ST gene **atm p53** cell proliferation cycle
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(TP53; genetic interactions between **atm** and **p53** influence cellular proliferation and irradiation-induced cell cycle checkpoints)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**atm**; genetic interactions between **atm** and **p53** influence cellular proliferation and irradiation-induced cell cycle checkpoints)
IT Cell cycle
Cell proliferation
(genetic interactions between **atm** and **p53** influence cellular proliferation and irradiation-induced cell cycle checkpoints)

L68 ANSWER 9 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:172866 HCAPLUS
DN 126:262107
ED Entered STN: 14 Mar 1997
TI The **ataxia-telangiectasia** gene product, a constitutively expressed nuclear protein that is not up-regulated following genome damage
AU Brown, Kevin D.; Ziv, Yael; Sadanandan, Sunanda N.; Chessa, Luciana; Collins, Francis S.; Shiloh, Yosef; Tagle, Danilo A.
CS Lab. Gene Transfer, Natl. Human Genome Res. Inst., Bethesda, MD, 20892, USA

SO Proceedings of the National Academy of Sciences of the United States of America (**1997**), 94(5), 1840-1845
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
CC 13-1 (Mammalian Biochemistry)
Section cross-reference(s): 1, **8**, **9**

AB The product of the **ataxia-telangiectasia** gene (**ATM**) was identified by using an antiserum developed to a peptide corresponding to the deduced amino acid sequence. The **ATM** protein is a single, high-mol.-weight protein predominantly confined to the nucleus of human fibroblasts, but is present in both nuclear and microsomal fractions from human lymphoblast cells and peripheral blood lymphocytes. **ATM** protein levels and localization remain constant throughout all stages of the cell cycle. Truncated **ATM** protein was not detected in lymphoblasts from **ataxia-telangiectasia** patients homozygous for mutations leading to premature protein termination. Exposure of normal human cells to γ-irradiation and the radiomimetic drug neocarzinostatin had no effect on **ATM** protein levels, in contrast to a noted rise in **p53** levels over the same time interval. These findings are consistent with a role for the **ATM** protein in ensuring the fidelity of DNA repair and cell cycle regulation following genome damage.

ST **ataxia telangiectasia** gene protein subcellular localization; antiserum prepn **ATM** gene protein; DNA damage **ATM** gene protein

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**ATM**; subcellular localization of the **ataxia-telangiectasia** gene (**ATM**) product in human cells and its response to genome damage)

IT Nervous system
(**ataxia telangiectasia**; subcellular localization of the **ataxia-telangiectasia** gene (**ATM**) product in human cells and its response to genome damage)

IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(damage; subcellular localization of the **ataxia-telangiectasia** gene (**ATM**) product in human cells and its response to genome damage)

IT Antibodies
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(monoclonal, to **ATM** gene protein; subcellular localization of the **ataxia-telangiectasia** gene (**ATM**) product in human cells and its response to genome damage)

IT Lymphocyte
(peripheral blood; subcellular localization of the **ataxia-telangiectasia** gene (**ATM**) product in human cells and its response to genome damage)

IT Cell cycle
Cell nucleus
DNA repair
Fibroblast
Gamma ray
Lymphoblast
Microsome
(subcellular localization of the **ataxia-telangiectasia** gene (**ATM**) product in human cells and its response to genome damage)

IT **p53 (protein)**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(subcellular localization of the **ataxia-telangiectasia** gene (**ATM**) product in human cells and its response to genome damage)

IT 9014-02-2, Neocarzinostatin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(subcellular localization of the **ataxia-telangiectasia** gene (**ATM**) product in human cells and its response to genome damage)

L68 ANSWER 10 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:39666 HCAPLUS
DN 126:129960
ED Entered STN: 18 Jan 1997
TI DNA-dependent protein kinase is not required for accumulation of **p53** or cell cycle arrest after DNA damage
AU Rathmell, W. Kimryn; Kaufmann, William K.; Hurt, John C.; Byrd, Laura L.; Chu, Gilbert
CS Departments Medicine Biochemistry, Stanford University School Medicine, Stanford, CA, 94305, USA
SO Cancer Research (**1997**), 57(1), 68-74
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
CC 14-1 (Mammalian Pathological Biochemistry)
Section cross-reference(s): **8**, 13
AB In response to DNA damage, cells transduce a signal that leads to accumulation and activation of **p53** protein, transcriptional induction of several genes, including p21, gadd45, and gadd153, and cell cycle arrest. One hypothesis is that the signal is mediated by DNA-dependent protein kinase (DNA-PK), which consists of a catalytic subunit (DNA-PKcs) and a regulatory subunit (Ku). DNA-PK has several characteristics that support this hypothesis: Ku binds to DNA damaged by nicks or double-strand breaks, DNA-PKcs is activated when Ku binds to DNA, DNA-PK will **phosphorylate p53** and other cell cycle regulatory proteins in vitro, and DNA-PKcs shares homol. with **ATM**, which is mutated in **ataxia telangiectasia** and involved in signaling the **p53** response to ionizing **radiation.** The hypothesis was tested by analyzing early passage fibroblasts from severe combined immunodeficient mice, which are deficient in DNA-PK. After exposure to ionizing **radiation**, UV **radiation**, or Me methane-sulfonate, severe combined immunodeficient and wild-type cells were indistinguishable in their response. The accumulation of **p53**, induction of p21, gadd45, and gadd153, and arrest of the cell cycle in G1 and G2 occurred normally. Therefore, DNA-PK is not required for the **p53** response or cell cycle arrest after DNA damage.
ST DNA dependent protein kinase damage **p53**; **radiation** DNA dependent protein kinase **p53**
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(CDKN1A, induction; DNA-dependent protein kinase is not required for accumulation of **p53** or cell cycle arrest after DNA damage in relation to)
IT **p53 (protein)**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DNA-dependent protein kinase is not required for accumulation of

p53 or cell cycle arrest after DNA damage)
IT Ionizing **radiation**
Transcription, genetic
UV **radiation**
(DNA-dependent protein kinase is not required for accumulation of **p53** or cell cycle arrest after DNA damage in relation to)
IT Cell cycle
(arrest; DNA-dependent protein kinase is not required for accumulation of **p53** or cell cycle arrest after DNA damage)
IT DNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(damage; DNA-dependent protein kinase is not required for accumulation of **p53** or cell cycle arrest after DNA damage)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gadd153, induction; DNA-dependent protein kinase is not required for accumulation of **p53** or cell cycle arrest after DNA damage in relation to)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gadd45, induction; DNA-dependent protein kinase is not required for accumulation of **p53** or cell cycle arrest after DNA damage in relation to)
IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene gadd153, induction; DNA-dependent protein kinase is not required for accumulation of **p53** or cell cycle arrest after DNA damage in relation to)
IT **Proteins, specific or class**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene gadd45, induction; DNA-dependent protein kinase is not required for accumulation of **p53** or cell cycle arrest after DNA damage in relation to)
IT Cyclin dependent kinase inhibitors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(p21CIP1/WAF1, induction; DNA-dependent protein kinase is not required for accumulation of **p53** or cell cycle arrest after DNA damage in relation to)
IT 66-27-3, Methyl methane-sulfonate
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(DNA-dependent protein kinase is not required for accumulation of **p53** or cell cycle arrest after DNA damage in relation to)
IT 9026-43-1, Protein kinase (**phosphorylating**)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DNA-dependent; DNA-dependent protein kinase is not required for accumulation of **p53** or cell cycle arrest after DNA damage)

L68 ANSWER 11 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:725561 HCAPLUS
DN 126:46171
ED Entered STN: 11 Dec 1996
TI The DNA damage response in DNA-dependent protein kinase-deficient SCID mouse cells: replication protein A **hyperphosphorylation** and **p53** induction
AU Fried, Laura M.; Koumenis, Constantinos; Peterson, Scott R.; Green, Susannah L.; van Zijl, Pierre; Allalunis-Turner, Joan; Chen, David J.; Fishel, Richard; Giaccia, Amato J.; et al.

CS Dep. Radiation Oncol., Stanford Univ. Sch. Med., Stanford, CA, 94305, USA
SO Proceedings of the National Academy of Sciences of the United States of America (**1996**), 93(24), 13825-13830
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
CC 15-8 (Immunochemistry)
Section cross-reference(s): 3, 7
AB Severe combined immunodeficient (SCID) mice display an increased sensitivity to ionizing **radiation** compared with the parental, C.B.-17, strain due to a deficiency in DNA double-strand break repair. The catalytic subunit of DNA-dependent protein kinase (DNA-PKCS) has previously been identified as a strong candidate for the SCID gene. DNA-PK **phosphorylates** many proteins in vitro, including **p53** and replication protein A (RPA), two proteins involved in the response of cells to DNA damage. To determine whether **p53** and RPA are also substrates of DNA-PK in vivo following DNA damage, the authors compared the response of SCID and MO59J (human DNA-PKcs-deficient glioblastoma) cells with their resp. wild-type parents following ionizing **radiation.** The findings indicate that (i) **p53** levels are increased in SCID cells following ionizing **radiation**, and (ii) RPA p34 is **hyperphosphorylated** in both SCID cells and MO59J cells following ionizing **radiation.** The **hyperphosphorylation** of RPA p34 in vivo is concordant with a decrease in the binding of RPA to single-stranded DNA in crude exts. derived from both C.B-17 and SCID cells. These results suggest that DNA-PK is not the only kinase capable of **phosphorylating** RPA. The authors conclude that the DNA damage response involving **p53** and RPA is not associated with the defect in DNA repair in SCID cells and that the physiol. substrate(s) for DNA-PK essential for DNA repair has not yet been identified.
ST DNA protein kinase severe combined immunodeficiency; **p53** RPA DNA protein kinase SCID
IT DNA formation factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RP-A, p34 subunit; replication protein A **hyperphosphorylation** and **p53** induction in DNA damage response in DNA-dependent protein kinase-deficient SCID mouse cells)
IT Nervous system
(**ataxia telangiectasia**; replication protein A **hyperphosphorylation** and **p53** induction in DNA damage response in DNA-dependent protein kinase-deficient SCID mouse cells in relation to)
IT DNA
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(damage; replication protein A **hyperphosphorylation** and **p53** induction in DNA damage response in DNA-dependent protein kinase-deficient SCID mouse cells)
IT DNA repair
(double-strand break; replication protein A **hyperphosphorylation** and **p53** induction in DNA damage response in DNA-dependent protein kinase-deficient SCID mouse cells)
IT **Phosphorylation**, biological
(**hyperphosphorylation**; replication protein A **hyperphosphorylation** and **p53** induction in DNA damage response in DNA-dependent protein kinase-deficient SCID mouse cells)
IT Ionizing **radiation**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(replication protein A **hyperphosphorylation** and **p53**

induction in DNA damage response in DNA-dependent protein kinase-deficient SCID mouse cells)

IT **p53 (protein)**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(replication protein A **hyperphosphorylation** and **p53** induction in DNA damage response in DNA-dependent protein kinase-deficient SCID mouse cells)

IT Immunodeficiency
(severe combined; replication protein A **hyperphosphorylation** and **p53** induction in DNA damage response in DNA-dependent protein kinase-deficient SCID mouse cells)

IT 9026-43-1, Protein kinase (**phosphorylating**)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(DNA-dependent; replication protein A **hyperphosphorylation** and **p53** induction in DNA damage response in DNA-dependent protein kinase-deficient SCID mouse cells)

RE.CNT 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Allalunis-Turner, M; Radiat Res 1993, V134, P349 HCAPLUS
(2) Anderson, C; Crit Rev Eukaryotic Gene Expression 1992, V2, P283 HCAPLUS
(3) Anderson, C; Trends Biochem Sci 1993, V18, P433 HCAPLUS
(4) Biedermann, K; Proc Natl Acad Sci USA 1991, V88, P1394 HCAPLUS
(5) Blunt, T; Cell 1995, V80, P813 HCAPLUS
(6) Boubnov, N; Mol Cell Biol 1995, V15, P5700 HCAPLUS
(7) Brush, G; Proc Natl Acad Sci USA 1994, V91, P12520 HCAPLUS
(8) Carty, M; EMBO J 1994, V13, P2114 HCAPLUS
(9) Coverly, D; Nucleic Acids Res 1992, V20, P3873
(10) Din, S; Genes Dev 1990, V4, P968 HCAPLUS
(11) Dvir, A; J Biol Chem 1993, V268, P10440 HCAPLUS
(12) Fishel, R; J Cell Biochem 1992, V16B, P102
(13) Fulop, G; Nature (London) 1990, V347, P479 HCAPLUS
(14) Gottlieb, T; Cell 1993, V72, P131 HCAPLUS
(15) Hartley, K; Cell 1995, V82, P849 HCAPLUS
(16) Hartwell, L; Science 1994, V266, P1821 HCAPLUS
(17) Hendrickson, E; Genes Dev 1988, V2, P817 HCAPLUS
(18) Hendrickson, E; Proc Natl Acad Sci USA 1991, V88, P4061 HCAPLUS
(19) Henricksen, L; J Biol Chem 1994, V269, P24203 HCAPLUS
(20) Huang, L; Cancer Res 1996, V56, P2940 HCAPLUS
(21) Kastan, M; Cancer Res 1991, V51, P6304 HCAPLUS
(22) Kastan, M; Cell 1992, V71, P587 HCAPLUS
(23) Khanna, K; Oncogene 1993, V8, P3307 HCAPLUS
(24) Kirchgessner, C; Science 1995, V267, P1178 HCAPLUS
(25) Lees-Miller, S; Mol Cell Biol 1990, V10, P6472 HCAPLUS
(26) Lees-Miller, S; Mol Cell Biol 1992, V12, P5041 HCAPLUS
(27) Lees-Miller, S; Science 1995, V267, P1183 HCAPLUS
(28) Lieber, M; Cell 1988, V55, P7 HCAPLUS
(29) Liu, V; Mol Cell Biol 1993, V13, P7222 HCAPLUS
(30) Malynn, B; Cell 1988, V54, P453 HCAPLUS
(31) Meek, D; EMBO J 1990, V9, P3253 HCAPLUS
(32) Meek, D; Semin Cancer Biol 1994, V5, P203 HCAPLUS
(33) Milne, D; J Biol Chem 1994, V269, P9253 HCAPLUS
(34) Milne, D; J Biol Chem 1995, V270, P5511 HCAPLUS
(35) Milne, D; Nucleic Acids Res 1992, V20, P5565 HCAPLUS
(36) Milne, D; Oncogene 1992, V7, P1361 HCAPLUS
(37) Moore, S; Proc Natl Acad Sci USA 1991, V88, P9067 MEDLINE
(38) Pan, Z; Proc Natl Acad Sci USA 1994, V91, P8343 HCAPLUS
(39) Pan, Z; Proc Natl Acad Sci USA 1995, V92, P4636 HCAPLUS
(40) Peterson, S; Proc Natl Acad Sci USA 1995, V92, P3171 HCAPLUS
(41) Savitsky, K; Science 1995, V268, P1749 HCAPLUS
(42) Seroussi, E; J Biol Chem 1993, V268, P7147 HCAPLUS
(43) Stillman, B; Annu Rev Cell Biol 1989, V5, P197 HCAPLUS

(44) Wang, Y; Proc Natl Acad Sci USA 1992, V89, P4231 HCAPLUS

L68 ANSWER 12 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:526299 HCAPLUS
DN 125:211997
ED Entered STN: 31 Aug 1996
TI Induction of **p53** and increased sensitivity to cisplatin in **ataxia-telangiectasia** cells
AU Zhang, Ning; Song, Qizhong; Lu, Hong; Lavin, Martin F.
CS PO Royal Bristbane Hospital, Queensland Institute of Medical Research, Brisbane, Australia
SO Oncogene (**1996**), 13(3), 655-659
CODEN: ONCNES; ISSN: 0950-9232
PB Stockton
DT Journal
LA English
CC 1-6 (Pharmacology)
Section cross-reference(s): 14
AB Several reports have demonstrated a defective **p53** response to ionizing **radiation** exposure in **ataxia-telangiectasia** (A-T) cells. On the other hand, **p53** induction was normal after u.v. irradiation, an agent to which A-T cells are not hypersensitive. We show here that A-T cells are more sensitive than normal lymphoblastoid cells to cisplatin treatment but the rate of induction of **p53** by cisplatin is similar in both cell types. In addition, the half-life of **p53**, both in the induced and uninduced forms, is the same in A-T and normal lymphoblastoid cells. The use of a reporter **assay** to deermine the functional status of **p53** confirmed the results obtained in the induction expts. with cisplatin. These results demonstrate that **p53** induction status in A-T cells does not correlate with sensitivity to the inducting agent and there is no inherent defect in the turn-over of **p53** in the induced or uninduced states in A-T.
ST cisplatin apoptosis **p53 ataxia telangiectasia**
IT Apoptosis
Drug resistance
(**p53** induction and increased sensitivity to cisplatin in human **ataxia-telangiectasia** cells)
IT Nervous system
(disease, **ataxia telangiectasia**, **p53** induction and increased sensitivity to cisplatin in human **ataxia-telangiectasia** cells)
IT **Phosphoproteins**
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**tumor suppressor**, **p53**, **p53** induction and increased sensitivity to cisplatin in human **ataxia-telangiectasia** cells)
IT 15663-27-1, Cisplatin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**p53** induction and increased sensitivity to cisplatin in human **ataxia-telangiectasia** cells)

L68 ANSWER 13 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:937720 HCAPLUS
DN 123:336328
ED Entered STN: 22 Nov 1995
TI Diminished capacity for **p53** in mediating a **radiation**-induced G1 arrest in established human tumor cell lines
AU Li, Chuan-Yuan; Nagasawa, Hatsumi; Dahlberg, William K.; Little, John B.

CS Department of Cancer Biology, Harvard School of Public Health, Boston, MA, 02115, USA
SO Oncogene (**1995**), 11(9), 1885-92
CODEN: ONCNES; ISSN: 0950-9232
PB Stockton
DT Journal
LA English
CC 14-1 (Mammalian Pathological Biochemistry)
AB It has been reported that the **p53** gene mediates an ionizing **radiation**-induced G1 arrest in mammalian cells. To further characterize this important phenomenon, a panel of seven human diploid fibroblast cell strains and 14 human tumor cell lines from a variety of sources with both wild-type and mutant **p53** status were **assayed** for their susceptibility to G1 arrest after γ-ray irradiation by a continuous labeling [3H]thymidine incorporation technique. An irreversible G1-block involving 20-70% of the cell population was observed in diploid fibroblasts **irradiated** with 4 Gy. The block was abolished by transfection with the human papilloma virus E6 gene and in an **ataxia telangiectasia** (AT) cell line, indicating a role for the AT and **p53** genes resp. in this process. In contrast to wild-type normal fibroblast cell strains, the G1-block in all tumor cell lines was significantly reduced, irresp. of their **p53** status. None of the nine human tumor cell lines with mutant **p53** genes showed a significant G1-block following irradiation with 4 Gy. Among the five tumor cell lines expressing wild-type **p53**, two showed no apparent G1-block. The remaining three showed a G1-block involving only 8-15% of the cell population, a block much smaller in magnitude than that seen in diploid fibroblasts. Finally, a diploid fibroblast cell strain and a tumor cell line, both showing a normal **p53** and p21/WAF1 expression pattern, were examined for pRb **phosphorylation** before and after irradiation The diploid fibroblast cell strain showed a significant G1-arrest and a clear inhibition of pRb **phosphorylation** by irradiation whereas the tumor cells showed no G1-arrest and no inhibition of pRb **phosphorylation.** These results suggest that (1) multiple genetic factors may modulate the occurrence and magnitude of the G1-arrest induced by exposure to ionizing **radiation**, (2) the capacity for **p53** to mediate a **radiation**-induced G1 arrest is significantly reduced in tumor cells, (3) the disruption of G1-block modulating factor(s) other than **p53** may be an important step in carcinogenesis.
ST **p53** suppressor **radiation** cell cycle tumor
IT **Phosphorylation**, biological
(of retinoblastoma protein in relation to **p53**-independent **radiation**-induced arrest of human tumor cell lines)
IT Cell cycle
Gamma ray
Neoplasm
(**p53**-dependent and -independent mediation of **radiation**-induced cell cycle arrest of human tumor cell lines)
IT Ribonucleic acid formation factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene Rb, **phosphorylation** of retinoblastoma protein in relation to **p53**-independent **radiation**-induced arrest of human tumor cell lines)
IT **Phosphoproteins**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**tumor suppressor**, **p53**, **p53** -dependent and -independent mediation of **radiation**-induced cell cycle arrest of human tumor cell lines)

L68 ANSWER 14 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:774060 HCAPLUS

DN 123:225174
ED Entered STN: 02 Sep 1995
TI Nature of G1/S cell cycle checkpoint defect in **ataxia-telangiectasia**
AU Khanna, Kum Kum; Beamish, Heather; Yan, Jun; Hobson, Karen; Williams, Richard; Dunn, Ian; Lavin, Martin F.
CS Queensland Cancer Fund Res. Unit., Queensland Inst. of Medical Res., Queensland, 4029, Australia
SO Oncogene (**1995**), 11(4), 609-18
CODEN: ONCNES; ISSN: 0950-9232
PB Stockton
DT Journal
LA English
CC 14-14 (Mammalian Pathological Biochemistry)
Section cross-reference(s): **8**
AB The authors have previously demonstrated that cells from patients with **ataxia-telangiectasia** (A-T) fail to show initial delay at several cell cycle checkpoints post-irradiation In addition a defect in the induction of **p53** by ionizing **radiation** was evident. The authors demonstrate here that the **radiation** signal transduction pathway operating through **p53**, its target gene WAF1, cyclin-dependent kinases and the retinoblastoma (Rb) protein is defective in A-T cells. The defective **p53** induction after ionizing **radiation**, observed previously in A-T cells, was also reflected at the functional level using **p53**-DNA binding activity, transactivation and transfection with wild type **p53.** Correction of the defect at the G1/S checkpoint was observed when wild type **p53** was constitutively expressed in A-T cells. Exposure of control cells to **radiation** gave rise to **p53** induction and as a consequence increased expression of WAF1 mRNA and protein, but A-T cells were defective in this response. As expected the WAF1 response in **irradiated** control cells resulted in an inhibition of cyclin-dependent kinase activity including cyclin E-cdk2, which plays an important role in the transition from G1 to S phase. No inhibition of cyclin-dependent kinase activity was observed in A-T cells correlating with the delayed WAF1 response. On the contrary an enhancement of cyclin-dependent kinase activity was seen in A-T cells post-irradiation An accumulation of the **hypophosphorylated** form of Rb protein occurred in **irradiated** control cells compatible with the G1/S phase delay observed in these cells after exposure to **radiation.** In **unirradiated** A-T cells the amount of Rb protein was much higher compared to controls and it was mainly in the **hyperphosphorylated** (functionally inactive) form. In addition, accumulation of the **hypophosphorylated** form of Rb in A-T cells post-irradiation was defective, consistent with the lack of cell cycle arrest. Thus the failure of the G1/S checkpoint in A-T cells after exposure to ionizing **radiation** is consistent with a defective **radiation** signal transduction pathway operating through **p53.**
ST **p53** signal transduction **ataxia telangiectasia**
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(WAF1/CIP1; **radiation** signal transduction pathway through **p53**, gene WAF1, cyclin-dependent kinases and retinoblastoma protein is defective in **ataxia-telangiectasia** resulting in failure of G1/S cell cycle checkpoint after ionizing **radiation**)
IT **Proteins, specific or class**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(p21Cip1/WAF1; **radiation** signal transduction pathway through **p53**, gene WAF1, cyclin-dependent kinases and retinoblastoma

protein is defective in **ataxia-telangiectasia**)

IT Cell cycle
Signal transduction, biological
(**radiation** signal transduction pathway through **p53**, gene WAF1, cyclin-dependent kinases and retinoblastoma protein is defective in **ataxia-telangiectasia** resulting in failure of G1/S cell cycle checkpoint after ionizing **radiation**)

IT **Phosphoproteins**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cyclins A, complexes, with gene cdk2 phosphoprotein; **radiation** signal transduction pathway through **p53**, gene WAF1, cyclin-dependent kinases and retinoblastoma protein is defective in **ataxia-telangiectasia**)

IT **Phosphoproteins**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cyclins E, complexes, with gene cdk2 phosphoprotein; **radiation** signal transduction pathway through **p53**, gene WAF1, cyclin-dependent kinases and retinoblastoma protein is defective in **ataxia-telangiectasia**)

IT Nervous system
(disease, **ataxia telangiectasia**, **radiation** signal transduction pathway through **p53**, gene WAF1, cyclin-dependent kinases and retinoblastoma protein is defective in **ataxia-telangiectasia** resulting in failure of G1/S cell cycle checkpoint after ionizing **radiation**)

IT Ribonucleic acid formation factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene Rb, **radiation** signal transduction pathway through **p53**, gene WAF1, cyclin-dependent kinases and retinoblastoma protein is defective in **ataxia-telangiectasia** resulting in failure of G1/S cell cycle checkpoint after ionizing **radiation**)

IT **Phosphoproteins**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene cdk2, complexes, with cyclin A and cyclin E; **radiation** signal transduction pathway through **p53**, gene WAF1, cyclin-dependent kinases and retinoblastoma protein is defective in **ataxia-telangiectasia**)

IT **Radiation**
(ionizing, **radiation** signal transduction pathway through **p53**, gene WAF1, cyclin-dependent kinases and retinoblastoma protein is defective in **ataxia-telangiectasia** resulting in failure of G1/S cell cycle checkpoint after ionizing **radiation**)

IT **Phosphoproteins**
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**tumor suppressor**, **p53**, **radiation** signal transduction pathway through **p53**, gene WAF1, cyclin-dependent kinases and retinoblastoma protein is defective in **ataxia-telangiectasia** resulting in failure of G1/S cell cycle checkpoint after ionizing **radiation**)

IT 146279-88-1, CYCLIN A-cdk2 KINASE 146279-89-2, Cyclin E-cdk2 kinase 150428-23-2, Cyclin-dependent kinase

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**radiation** signal transduction pathway through **p53**, gene WAF1, cyclin-dependent kinases and retinoblastoma protein is defective in **ataxia-telangiectasia** resulting in failure of G1/S cell cycle checkpoint after ionizing **radiation**)

L68 ANSWER 15 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:500628 HCAPLUS
ED Entered STN: 20 Apr 1995
TI Defective G2 checkpoint function in cells from individuals with familial cancer syndromes
AU Paules, Richard S.; Levedakou, Eleni N.; Wilson, Sandra J.; Innes, Cynthia L.; Rhodes, Nelson; Tlsty, Thea D.; Galloway, Denise A.; Donehower, Lawrence A.; Tainsky, Michael A.; Kaufmann, William K.
CS Growth Control and Cancer Group, Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709, USA
SO Cancer Research (**1995**), 55(8), 1763-73
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB The early events in the G2 checkpoint response to ionizing **radiation** (IR) were analyzed in diploid normal human fibroblasts (NHFs) and fibroblasts from patients with two heritable cancer syndromes. Exposure to γ- **radiation** of asynchronously growing NHFs resulted in a rapid reduction in the number of cells in mitosis (G2 delay) and was accompanied by a quant. similar reduction in the p34CDC2/cyclin B in vitro histone H1 kinase activity as compared with sham-treated controls. This G2 delay was strong by 1 h following exposure to IR, maximal by 2 h, and was accompanied by an accumulation of tyrosine-**phosphorylated** p34CDC2 mols. In contrast, fibroblasts from individuals with **ataxia telangiectasia** displayed significantly less reduction of the mitotic index or histone H1 kinase activity after IR. Low passage fibroblasts from individuals with Li-Fraumeni syndrome having one wild-type and one mutated **p53** allele were similar to NHFs in their immediate G2 checkpoint response to IR, as were NHFs expressing the human papilloma virus type 16 E6 gene product (functionally inactivating **p53**) and low passage cells from **p53**-deficient mouse embryos. However, the **p53**-deficient fibroblasts were genomically unstable and became defective in their early G2 checkpoint response to IR. Furthermore, immortal Li-Fraumeni syndrome fibroblasts lacking wild-type **p53** displayed an attenuated G2 checkpoint response. These results link the early events in G2 checkpoint response to IR in NHFs with a rapid inhibition of p34CDC2/cyclin B protein kinase activity and demonstrate that while not required for this immediate G2 delay, lack of **p53** can lead to subsequent genetic alterations that result in defective G2 checkpoint function.

L68 ANSWER 16 OF 16 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:317512 HCAPLUS
DN 122:103134
ED Entered STN: 28 Jan 1995
TI Defect in **radiation** signal transduction in **ataxia-telangiectasia**
AU Lavin, M. F.; Khanna, K. K.; Beamish, H.; Teale, B.; Hobson, K.; Watters, D.
CS Queensland Cancer Fund Res. Unit, Queensland Inst. Med. Res., Brisbane, 4029, Australia
SO International Journal of Radiation Biology (**1994**), 66(6), S151-S156

CODEN: IJRBE7; ISSN: 0955-3002
PB Taylor & Francis
DT Journal
LA English
CC 14-10 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 8

AB Exposure of mammalian cells to ionizing **radiation** causes a delay in progression through the cycle at several checkpoints. Cells from patients with **ataxia-telangiectasis** (A-T) ignore these checkpoint controls postirradn. The tumor suppressor gene product **p53** plays a key role at the G1/S checkpoint preventing the progression of cells into S phase. The induction of **p53** by **radiation** is reduced and/or delayed in A-T cells, which appears to account for the failure of delay at the G1/S checkpoint. We have investigated further this defect **radiation** signal transduction in A-T. While the **p53** response was defective after **radiation**, agents that interfered with cell cycle progression such as mimosine, aphidicolin and deprivation of serum led to a normal **p53** response in A-T cells. None of these agents caused breaks in DNA, as determined by pulse-field gel electrophoresis, in order to elicit the response. Since this pathway is mediated by protein kinases, we investigated the activity of several of these enzymes in control and A-T cells. Ca+2-dependent and -independent protein kinase C activities were increased by **radiation** to the same extent in the two cell types, a variety of serine/threonine protein kinase activities were approx. the same and anti-tyrosine antibodies failed to reveal any differences in protein **phosphorylation** between A-T and control cells. It is not evident what is the nature of the defect in signal transduction in A-T cells. However, it is clear that the **p53** response is normal in these cells after exposure to some agents and it is mediated through protein kinase C or anther serine/threonine kinase.

ST **radiation** signal transduction **p53 ataxia telangiectasia**

IT Signal transduction, biological
(defect in **radiation** signal transduction in humans with **ataxia-telangiectasia**)

IT Cell cycle
(in **ataxia-telangiectasia** in humans)

IT **Phosphorylation**, biological
(in **radiation** signal transduction defect in humans with **ataxia-telangiectasia**)

IT Gene, animal
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(TP53, in **radiation** signal transduction defect in humans with **ataxia-telangiectasia**)

IT Nervous system
(disease, **ataxia telangiectasia**, **radiation** signal transduction defect in humans with)

IT **Radiation**
(ionizing, **radiation** signal transduction defect in humans with **ataxia-telangiectasia**)

IT **Phosphoproteins**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**tumor suppressor**, **p53**, in **radiation** signal transduction defect in humans with **ataxia-telangiectasia**)

IT 9026-43-1, Serine/threonine kinase 141436-78-4, Protein kinase C
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study);

PROC (Process)
(in **radiation** signal transduction defect in humans with **ataxia-telangiectasia**)

=> => fil wpix
FILE 'WPIX' ENTERED AT 13:12:52 ON 14 MAR 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE LAST UPDATED: 10 MAR 2004 <20040310/UP>
MOST RECENT DERWENT UPDATE: 200417 <200417/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE, PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE http://thomsonderwent.com/coverage/latestupdates/ <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER GUIDES, PLEASE VISIT:
http://thomsonderwent.com/support/userguides/ <<<

>>> ADDITIONAL POLYMER INDEXING CODES WILL BE IMPLEMENTED FROM DERWENT UPDATE 200403.
THE TIME RANGE CODE WILL ALSO CHANGE FROM 018 TO 2004.
SDIS USING THE TIME RANGE CODE WILL NEED TO BE UPDATED.
FOR FURTHER DETAILS: http://thomsonderwent.com/chem/polymers/ <<<

=> d all abeq tech abex tot

L84 ANSWER 1 OF 12 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-131346 [13] WPIX
DNC C2004-052554
TI Isolated nucleic acid molecule useful for treating cancer e.g. metastatic cancer and esophageal squamous cell carcinoma comprising specific nucleotide sequences.
DC B04 D16
IN ABRAHAM, R T; OTTERNESS, D M
PA (ABRA-I) ABRAHAM R T; (OTTE-I) OTTERNESS D M; (BURN-N) BURNHAM INST; (UYDU-N) UNIV DUKE
CYC 103
PI US 2003228675 A1 20031211 (200413)* 127p C12N009-12
WO 2003104475 A2 20031218 (200413) EN C12Q000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
ADT US 2003228675 A1 US 2002-165216 20020606; WO 2003104475 A2 WO 2003-US18126 20030606
PRAI US 2002-165216 20020606
IC ICM C12N009-12; C12Q000-00
ICS A61K031-522; C07H021-04; C12N005-06; C12N009-22; C12P021-02
AB US2003228675 A UPAB: 20040223
NOVELTY - An isolated **Ataxia telangiectasia** mutated (ATM) related kinase autotaxin (ATX) nucleic acid molecule which comprises the nucleotide sequences of 12464 nucleotides as given in the

specification, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a vector comprising the isolated nucleic acid molecule;

(2) a host cell comprising the vector;

(3) preparation of an ATX polypeptide involving:

(a) growing the host cell under suitable conditions for expression of the autotaxin (ATX) polypeptide; and

(b) isolating the ATX polypeptide from the host cell or host cell growth medium;

(4) an isolated oligonucleotide comprising at least 15 contiguous nucleotides of a nucleotide sequence agcaagctcc and ctcctgtctc;

(5) an isolated polypeptide comprising the amino acid sequence of 3521 amino acids as given in the specification;

(6) an antibody or its antigen binding fragment specifically binds to an ATX polypeptide comprising an amino acid sequence of 3521 amino acids as given in the specification;

(7) **identification** of a compound that specifically binds to an ATX polypeptide involving contacting the ATX polypeptide with polypeptide and determining specific binding of polypeptide to the ATX polypeptide;

(8) **identification** of an ATX-modulatory compound (preferably interfering RNA) involving measuring the level of an ATX polypeptide in the presence of a test compound (where the difference in the level of the ATX polypeptide in presence of the test compound compared to in the absence of the test compound indicating that test compound is an ATX-modulatory compound). The ATX-modulatory compound is other than caffeine or wortmannin; and

(9) modulation of cell survival involving introduction of interfering RNA into a cell.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - **Ataxia telangiectasia** mutated (ATM) related kinase autotaxin (ATX) inhibitor.

USE - For treating cancer (e.g. metastatic cancer, human soft tissue carcinomas, esophageal squamous cell carcinoma, blood cell malignancies, thymic lymphoma lung cancer, breast cancer (including small cell carcinoma and ductal carcinoma), gastrointestinal cancer (including stomach cancer, colon cancer and colorectal cancer).

ADVANTAGE - The ATX-modulating compound increases or decreases the level of ATX polypeptide. The interfering RNA increases or decreases the cell survival.

Dwg.0/6

FS CPI

FA AB

MC CPI: B04-B04C2; B04-C01G; B04-E02F; B04-E03F; B04-E05; B04-E08; B04-F0100E; B04-G05; B04-L0100E; B04-M01; B04-N02A0E; B11-A; B11-C07A; B11-C08E; B11-C08F2; B11-C08F4; B11-C10; B12-K04A1; B12-K04E; B12-K04F; B14-H01; B14-L01; B14-L06; B14-S03; D05-A02; D05-C12; D05-H07; D05-H08; D05-H09; D05-H11; D05-H12A; D05-H12D1; D05-H14; D05-H17A6; D05-H18; D05-H19

TECH UPTX: 20040223

TECHNOLOGY FOCUS - BIOTECHNOLOGY - The nucleic acid molecule encodes an ATX polypeptide comprising an amino acid sequence of 3521 amino acids as given in the specification.

Preferred Method: The level of ATX polypeptide is measured by determining the kinase activity of the ATX polypeptide, phosphorylation of a **p53** polypeptide or its fragment, level of **p53** polypeptide accumulation, or non-sense mediated messenger RNA (mRNA) decay (NMD). The cell is exposed to a stressor agent selected from UV light, ionizing radiation or a chemical agent.

ABEX UPTX: 20040223

ADMINISTRATION - Administration is topically, intraocularly, intradermally, parenterally, orally, intranasally, intravenously, intramuscularly, intraspinally, intracerebrally, or subcutaneously.

No dosage details given.

EXAMPLE - No relevant example given.

L84 ANSWER 2 OF 12 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-766153 [72] WPIX
CR 2003-567379 [53]
DNN N2003-613679 DNC C2003-210477
TI **Identifying** the activated state of **ataxia-telangiectasia** mutated kinase, e.g. for detecting DNA damage, comprises determining the phosphorylation state of serine-1981.
DC B04 D16 S03
IN BAKKENIST, C; KASTAN, M B
PA (BAKK-I) BAKKENIST C; (KAST-I) KASTAN M B
CYC 1
PI US 2003157572 A1 20030821 (200372)* 16p G01N033-53
ADT US 2003157572 A1 CIP of US 2002-307077 20021127, US 2003-351733 20030124
PRAI US 2003-351733 20030124; US 2002-307077 20021127
IC ICM G01N033-53
ICS C12N009-12; G01N033-537; G01N033-543; G01N033-567
AB US2003157572 A UPAB: 20031107
NOVELTY - **Identifying** the activated state of **ataxia-telangiectasia** mutated kinase (M1) comprising determining the phosphorylation state of serine-1981, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) antibody that specifically recognizes the phosphorylation state of serine-1981 of **ataxia-telangiectasia** mutated (**ATM**) **kinase**;

(2) detecting DNA damage (M2) in a sample by **identifying** the activated state of **ATM kinase** as above;

(3) detecting a DNA-damaging agent (M3) in a sample by contacting an cell containing **ATM kinase** with the sample and **identifying** the activated state of the **ATM kinase** as above;

(4) kit for detecting a DNA-damaging agent, comprising an antibody as above;

(5) production of soluble **ATM kinase** (M4) or a fragment thereof by contacting a polypeptide containing the **ATM kinase** domain with a polypeptide containing serine-1981 of **ATM kinase**;

(6) **identifying** an agent (M5) that modulates the activated state of **ATM kinase** by contacting an cell containing **ATM kinase** with an agent and **identifying** the activated state of the **ATM kinase** as above;

(7) enhancing a cellular response to DNA damage by administering an agent (I) that agonizes the activation of **ATM kinase**;

(8) **identifying** an agent (M6) that inhibits **ATM kinase** activity by contacting soluble **ATM kinase** protein with the agent and a phosphate donor and determining the phosphorylation state of serine-1981.

USE - The method is useful for detecting DNA damage and DNA-damaging agents, **identifying** agents that modulate the activated state of **ATM kinase** and **identifying** agents that inhibit **ATM kinase** activity (claimed).

Dwg.0/0
FS CPI EPI
FA AB; DCN
MC CPI: B04-C01G; B04-E03E; B04-F01; B04-G03; B04-G21; B04-G22; B04-L0100E; B04-N02A0E; B11-C07A3; B11-C07A4; B11-C07A5; B12-K04; B12-K04E; D05-H08; D05-H09; D05-H11; D05-H12A; D05-H12D6; D05-H13; D05-H17B3
EPI: S03-E14H4
TECH UPTX: 20031107

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: In (M1) the cell is from a biological sample. The phosphorylation state of the serine is determined using an antibody which specifically recognizes the phosphorylation state of the serine. The antibody is detected using an immunoassay comprising enzyme-linked immunosorbent, immunodiffusion, chemiluminescent, immunofluorescent, immunohistochemical, radioimmunoassay, agglutination, complement fixation, immunoelectrophoresis, western blots, mass spectrometry, antibody array or immunoprecipitation assays. In (M2) the sample is a biopsy sample, tissue, cell or fluid and is obtained from a subject exposed to radiation therapy or chemotherapy. In (M3) the sample is a biological or environmental sample. In (M4) the first and second polypeptide are produced separately or produced as a single polypeptide and in the same cell. In (M5) the agent agonizes the activation of **ATM kinase.**
Preferred Kit: The kit further comprises **ATM kinase.**
Preferred Antibody: This is a poly- or monoclonal antibody or antibody fragment that specifically recognizes phosphorylated or nonphosphorylated serine-1981.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Agent: (I) antagonizes or enhances the activation of **ATM kinase.** (I) is preferably chloroquine or trichostatin A, a radioprotectant, a cancer chemopreventive (especially acting via **p53** activation) or an anti-aging agent.

ABEX UPTX: 20031107
EXAMPLE - Phosphorylated serine-1981 of **ataxia-telangiectasia** mutated kinase was detected using antibodies produced by immunizing rabbits with a keyhole limpet cyanin (KLH) conjugate of the synthetic peptide Ser-Leu-Ala-Phe- Glu-Glu-Gly-Ser-Pro-Gln-Ser-Thr-Thr-Ile-Ser-Ser.

L84 ANSWER 3 OF 12 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-232383 [23] WPIX
CR 1999-073587 [07]
DNC C2003-059869
TI Assay for compound affecting DNA binding by **ataxia-telangiectasia** mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining binding of the gene and DNA.
DC B04 D16
IN **JACKSON, S P; LAKIN, N D; SMITH, G C M**
PA (KUDO-N) KUDOS PHARM LTD
CYC 1
PI GB 2362952 A 20011205 (200323)* 129p C12Q001-48
GB 2362952 B 20020306 (200326) C12Q001-48
ADT GB 2362952 A Derived from GB 1998-15423 19980716, GB 2001-20368 20010821;
GB 2362952 B Derived from GB 1998-15423 19980716, GB 2001-20368 20010821
PRAI GB 1997-14971 19970716
IC ICM C12Q001-48
ICS C07K014-47; C12N009-12
AB GB 2362952 A UPAB: 20030428
NOVELTY - Assay (M1) for a compound able to affect DNA binding by **ataxia-telangiectasia** mutated (ATM) gene or a protein having an associated kinase activity,comprising bringing into contact ATM or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining binding of ATM and DNA in the presence of the test compound, is new.
DETAILED DESCRIPTION - Assay (M1) for a compound able to affect DNA binding by **ataxia-telangiectasia** mutated (ATM) gene or a protein having an associated kinase activity, involves bringing into contact a substance which is ATM or a protein having an associated kinase activity, or its fragment, variant or derivative which is able to bind DNA and a test compound, under conditions, where in the absence of the test

compound being an inhibitor of DNA binding by ATM or the protein having an associated kinase activity, the substance binds DNA, and determining binding between the substance and the DNA.

INDEPENDENT CLAIMS are also included for the following:

(1) an agent (I) capable of affecting DNA binding by ATM obtained using M1;

(2) purifying (M2) ATM or related kinase such as ATR, by contacting a mixture of molecules including ATM or ATR with DNA or n-(5-amino-1-carboxypentyl)imino-diacetic acid (NTA), washing molecules which do not bind a DNA or NTA, and recovering ATM or ATR from the DNA- or NTA-bound fraction;

(3) use of DNA (II) for purifying ATM or ATR; and

(4) a substantially pure ATM (III) or ATR (IV).

ACTIVITY - Anti-HIV; Cytostatic; Antipsoriatic; Antitumor. No biological dats is given.

MECHANISM OF ACTION - Modulator of ATM (claimed); Regulator of immune system function; Inhibitor of cell proliferation; Modulator of interaction of ATM with **p53** protein. No supporting data is given.

USE - M1 is useful for assaying for a compound able to affect DNA binding by ATM or a protein having an associated kinase activity. (I) is useful in therapy involving modulating ATM action or in the manufacture of a medicament for modulating ATM action. (II) is useful for purifying ATM or ATR (all claimed). (I) is also useful for treating humans with **ataxia-telangiectasia**, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for inhibiting cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumors, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy.

Dwg.0/11

FS CPI

FA AB; DCN

MC CPI: B04-E03; B04-E03B; B04-E03E; B04-E04; B04-F0100E; B10-B02J; B11-C08E5; B12-K04; B12-K04E; B12-K04F; D05-H08; D05-H09; D05-H12B1; D05-H12B2; D05-H12D5; D05-H13; D05-H14

TECH UPTX: 20030407

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: In M1, the protein having an associated kinase activity is DNA-protein kinase (PK) or ATR. In M2, the mixture is contacted with NTA in the presence of Ni2+.

ABEX UPTX: 20030407

WIDER DISCLOSURE - Also disclosed as new are the following:

(1) a peptide fragment of ATM which is able to interact with **p53** and/or inhibit interaction between ATM and **p53**;

(2) a peptide fragment of **p53** which is able to interact with ATM and/or inhibit interaction between ATM and **p53**;

(3) a peptide which is a sequence variant or derivative of a wild type ATM or **p53** sequence, but which retains ability to interact with **p53** or ATM and/or ability to modulate interaction between ATM and **p53**;

(4) a substance, which may be a single molecule or a composition including two or more components, which includes a peptide fragment of ATM or **p53**;

(5) a derivative of the peptide fragment of ATM or **p53**;

(6) a nucleic acid encoding ATM or **p53**;

(7) making ATM or **p53** polypeptide or peptide;

(8) a host cell containing the nucleic acid of (6);

(9) introducing the nucleic acid encoding ATM or **p53** into the host cell of (8);

(10) an assay method for a substance with ability to modulate, e.g. disrupt or interfere with interaction between ATM and **p53**;

(11) an assay method for a substance able to interact with the relevant

region of ATM or **p53**;
(12) an assay method for a substance able to affect **p53** activity;
(13) a pharmaceutical composition, medicament, drug or other composition comprising (I); and
(14) making the pharmaceutical composition of (13).

ADMINISTRATION - The composition comprising (I) is administered by oral, cutaneous, subcutaneous or intravenous route. No dosage details are given.

EXAMPLE - One DNA strand containing a 5' biotin group was annealed with complementary oligonucleotide(s) such as 5'-B-CCTGCCCTTGCCTGA-3', and bound to streptavidin-coated iron-oxide particles. HeLa nuclear extract, or **ataxia-telangiectasia** mutated gene (ATM) enriched extract was incubated on ice for 30 minutes with the DNA-iron oxide particles. After washing with 5x0.5 ml of Dasterisk buffer (25 mM HEPES-KOH, pH 7.6, 20% glycerol, 2 mM MgCl2, 0.2 mM EDTA, 1 mM dithiothreitol (DTT), 0.5 mM phenylmethanesulfonylfluoride (PMSF), 1 mM Na Metabisulfite) containing 50 mM KCl, protein was eluted with 500 mM KCl Dasterisk buffer or in gradual stepwise manner with KCl concentrations of 100 mM, 250 mM and 500 mM in buffer Dasterisk. Fractions were analyzed for ATM protein content by Western blotting using a rabbit polyclonal antisera raised against amino acid residues. All steps were performed at 4degreesC. HeLa nuclear extract was applied to a Q-Sepharose column equilibrated in Dasterisk buffer. After washing with 2 column volume of 50 mM KCl Dasterisk, protein was eluted with a continuous salt gradient of 50 mM-500 mM KCl. Fractions containing ATM and devoid of DNA-protein kinase (PK) were pooled and, after diluting to 100 mM KCl in Dasterisk buffer, were loaded onto a heparin agarose column pre-equilibrated in 100 mM KCl Dasterisk buffer. The column was washed with 2 column volume of 100 mM KCl Dasterisk buffer before eluting with a continuous gradient of 50 mM-500 mM KCl in buffer Dasterisk. ATM was again followed by Western blot analysis and eluted between 200 and 220 mM KCl. Peak fractions were pooled and dialyzed against 50 mM buffer Dasterisk. Peak ATM fractions were then incubated with gentle mixing for 1 hour with 200 mug biotinylated 50 base pair double stranded (ds) DNA conjugated to streptavidin iron-oxide particles. Unbound protein was rebound to fresh DNA-iron oxide particles. Particles were collected by a magnet and were washed 5x with 0.5 ml of 50 mM KCl Dasterisk buffer before eluting ATM with 2x75 microl 500 mM KCl buffer Dasterisk. Purified ATM was snap-frozen and stored at -70degreesC.

L84 ANSWER 4 OF 12 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-739588 [80] WPIX
CR 2003-531723 [50]
DNC C2002-209337
TI Novel nucleic acid encoding human E6-targeted protein 1 isoform, for treating hyperproliferative and neurodegenerative disorders, inflammatory and allergic diseases, autoimmune diseases and atherosclerosis.
DC B04 D16
IN BAND, V; GAO, Q
PA (NEWE-N) NEW ENGLAND MEDICAL CENT INC
CYC 1
PI US 6440696 B1 20020827 (200280)* 73p C12N015-00
ADT US 6440696 B1 US 1999-362336 19990728
PRAI US 1999-362336 19990728
IC ICM C12N015-00
ICS C07H021-04; C12N005-00; C12N015-63
AB US 6440696 B UPAB: 20030805
NOVELTY - An isolated nucleic acid (I) encoding a human E6-targeted protein 1 (E6TP1) isoform, where the isoform binds to human papillomavirus E6 protein and comprises amino acids 489-819 of a sequence (S1) of 1783 amino acids defined in the specification, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the

following:

(1) a host cell (II) transformed with an expression vector encoding an E6TP1 polypeptide comprising (S1) or amino acids 489-819 of (S1), or a sequence (S2) of 1804 amino acids defined in the specification; and

(2) producing an isolated E6TP1 protein, by culturing a host cell transformed with an expression vector comprising (I), expressing the nucleic acid to produce an E6TP1 protein, and recovering the expressed protein.

ACTIVITY - Cytostatic; Antiinflammatory; Cardiant; Immunosuppressive; Antiallergic; Anti-tumor; Antiatherosclerotic; Hepatotropic; Antipsoriatic; Vulnerary; Immunomodulator; Vasotropic; Antianemic; Virucide; Osteopathic; Osteoarthritic.

No biological data given.

MECHANISM OF ACTION - Regulator of small G-protein signaling pathways; Regulator of cell proliferation; Gene therapy.

No biological data given.

USE - (I) is useful for treating hyperproliferative disorders such as tumors, cancers and malignancies, degenerative disorders such as neurodegenerative disorders and osteoarthritis, disorders associated with organ transplantation, inflammatory and allergic diseases, autoimmune diseases, atherosclerosis, cirrhosis, psoriasis, scarring, nephropathy, and cardiac and muscle diseases, HPV associated or non-HPV associated diseases and carcinomas.

(I) is useful as makers for specific disease states such as neurodegenerative disorders, autoimmune diseases, inflammatory and allergic diseases, and hyperproliferative disorders, that involves the disruption of physiological processes in which E6TP1 and E6TP1-IP are involved. (I) is useful as hybridization probes, and in assays for detecting, prognosing, diagnosing or monitoring various conditions associated with aberrant levels of E6TP1, E6TP1-IP or their complex.

(I) is also useful for treating pre-malignant conditions and/or for preventing progression of pre-malignancy to a neoplastic or malignant state; and for treating a patient who exhibits predisposing factors e.g. showing a Mendelian inheritance pattern (e.g. **ataxia telangiectasia**, Chediak-Higashi's syndrome, Fanconi's aplastic anemia and Bloom's syndrome), and infection with virus e.g. HPV.

Dwg.0/7

FS CPI

FA AB; DCN

MC CPI: B04-C01E; B04-E03F; B04-F0100E; B04-N02A0E; B14-A02; B14-C01; B14-C03; B14-F01; B14-F03; B14-F07; B14-G02A; B14-G02C; B14-H01; B14-J01; B14-J05; B14-N01; B14-N12; B14-N17C; D05-H08; D05-H12A; D05-H14; D05-H17A6

TECH UPTX: 20021212

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Protein: The isoform comprises (S1) or (S2), or amino acids 947-1018, 1705-1779 of (S1), or 1726-1790 of (S2), or the sequence AYSYRGPQDFNSFVLEQHEYT.

Preferred Nucleic Acid: (I) comprises the coding region of a sequence of 5965 (S3) or 6028 (S4) bp defined in the specification, or nucleotides 1813-2805, 3187-3403 or 5461-5685 of (S3), or 5524-5718 of (S4). (I) further comprises a transcriptional promoter, transcription terminator, an origin of replication, selectable marker, transcription enhancer element, transcription repressor element, or an artificial splice site.

ABEX UPTX: 20021212

WIDER DISCLOSURE - Also disclosed are:

(1) E6TP1 amino acid sequences;

(2) fragments, derivatives, analogs or homologs of (I), and the above sequences;

(3) cells containing (I) and the amino acid sequences of E6TP1;

(4) recombinant animal models comprising the above cells;

(5) anti-E6TP1 specific antibodies and its derivatives, fragments or analogs;

(6) isolation and purification of E6TP1 protein;

(7) oligonucleotides hybridizable to sense or antisense E6TP1 nucleic acids;
(8) antisense nucleic acids to (I);
(9) nucleic acids hybridizable to (I);
(10) inverse complement to the above nucleic acid of (9);
(11) E6TP1 and E6TP1-interacting proteins (E6TP1-IP proteins) and its derivatives, fragments, homologs, or analogs;
(12) nucleotide sequences encoding E6TP1 and E6TP1-IP derivatives or analogs;
(13) derivatives of complexes of E6TP1 fragments, derivatives or analogs that are differentially modified during or after translation;
(14) chimeric or fusion proteins containing E6TP1 protein and human papilloma virus E6 (HPV E6);
(15) **screening** E6TP1, E6TP1-IP and/or E6TP1:E6TP1-IP complexes and its derivatives, fragments or analogs for the ability to modulate cellular functions;
(16) kits containing anti-E6TP1, anti-E6TP1-IP and/or anti-E6TP1:anti-E6TP1-IP complex antibody; nucleic acids encoding E6TP1, E6TP1-IP and/or their complex; or a pair of oligonucleotide primers; and
(17) pharmaceutical composition comprising E6TP1 or E6TP1-IP.

SPECIFIC SEQUENCES - (I) comprises a sequence of 5965 or 6028 bp defined in the specification, or its complement (claimed).

ADMINISTRATION - Administered by intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, rectal, local, systemic, intraventricular, intrathecal or pulmonary route. Dosage for intranasal route is 0.01 pg/kg-1 mg/kg, and for intravenous route is 20-500 mug/kg.

EXAMPLE - Human papilloma virus 16 (HPV16) E6 interacting protein was **identified** using the yeast two-hybrid system. mRNA purified from normal mammary epithelial cell (MEC) strain 76N was used to synthesize cDNA. The cDNA was cloned into the EcoRI site of pGAD10, and a library of 1.5 x 10 (to the power of 6) primary recombinants with an average insert size of 1.5 kb was obtained. The bait plasmid pGBT9-E6 was constructed by cloning the polymerase chain reaction (PCR)-derived HPV16 E6 residues 2-158 as a SalI-SmaI fragment into pGBT9. The two-hybrid library **screen** was performed according to the Matchmaker two-hybrid system protocol to **identify** E6-interacting proteins. Saccharomyces cerevisiae yeast strain CG-1945 (five transformations) or HF7c (one transformation) were simultaneously transformed with pGBT9-E6 and the pGAD10 library DNA. HPV16 E6 interacting proteins were **identified** by growth on Trp-, Leu- and His- selection medium and positive beta-gal activity. Out of a total of 3.96 x 10 (to the power of 6) transformant clones **screened** in 6 transformations, 221 colonies grew on selection medium and 91 of these were positive in a subsequent beta-gal assay. To **identify** E6-interacting proteins among these 91 clones, an interaction assay was performed with pGB9-E6 versus two control baits that included human lamin or murine **p53** fused to Gal4 in pGBT9. Twenty eight clones were found to interact with HPV16 E6 specifically, and were subsequently sequenced. Of these 28 clones, one weakly positive clone encoded the 476 carboxyl-terminal amino acids of E6-AP, a known E6-binding protein, including its 18 amino acid E6-binding motif. A set of 11 **identical** and one distinct strongly positive clones that **identified** a single overlapping region (194 and 378 carboxyl terminal amino acid residues, respectively) of a single cDNA of a novel polypeptide were obtained. This novel protein was E6TP1 (E6-targeted protein 1). In addition, the remaining 15 clones encoded 1 known and 4 novel proteins. To obtain a full-length cDNA for E6TP1, a combination of DNA-hybridization **screening** of the 76N pGAD10 library and Marathon PCR cloning from normal mammary gland cDNA was utilized. A 5965 bp cDNA predicting a 1783 amino acid polypeptide (E6TP1alpha) was obtained

using these strategies. The size of this cDNA and the presence of several in-frame stop codons 5' to the initiation methionine indicated that this cDNA represented the major 6 kb transcript expressed in 76N MEC cell strain. One cDNA library-derived clone revealed a 63 bp in-frame insertion after nucleotide 3993, predicting a 1804 amino acid polypeptide (which was encoded by a nucleotide sequence of 6028 bp defined in the specification).

L84 ANSWER 5 OF 12 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-496922 [54] WPIX
DNC C2001-149280
TI Novel nucleic acid molecule e.g., ribozymes or antisense nucleic acid molecules, which downregulates expression of a **checkpoint kinase**-1 gene, useful for treating colorectal, lung, breast or prostate cancers.
DC B04 D16
IN BOOHER, R N; FATTAEY, A R; HOLMAN, P S; JARVIS, T; MCSWIGGEN, J
PA (FATT-I) FATTAEY A R; (ONYX-N) ONYX PHARM; (RIBO-N) RIBOZYME PHARM INC; (WARN) WARNER LAMBERT CO; (ONYX-N) ONYX PHARM INC
CYC 94
PI WO 2001057206 A2 20010809 (200154)* EN 115p C12N015-11
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001039740 A 20010814 (200173) C12N015-11
US 2003087847 A1 20030508 (200337) A61K048-00
ADT WO 2001057206 A2 WO 2001-US3504 20010202; AU 2001039740 A AU 2001-39740 20010202; US 2003087847 A1 Provisional US 2000-179983P 20000203, US 2001-776474 20010202
FDT AU 2001039740 A Based on WO 2001057206
PRAI US 2000-179983P 20000203; US 2001-776474 20010202
IC ICM A61K048-00; C12N015-11
ICS A61K031-7088; C07H021-00; C07H021-02; C12N005-10; C12N009-00; C12Q001-68
ICA A61P035-00
AB WO 200157206 A UPAB: 20010924
NOVELTY - A nucleic acid molecule (I) which downregulates expression of a **checkpoint kinase** (Chk)-1 gene, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a mammalian cell (II) including (I);

(2) an expression vector (III) comprising a nucleic acid sequence comprising (I), in a manner which allows expression of (I); and

(3) a mammalian cell (IV) including (III).

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - Antisense therapy; gene therapy; Chk1 gene expression downregulator; Chk1 gene expression inhibitor.

Antisense nucleic acid molecules (GeneBlocs) targeted to the human Chk1 RNA were tested for cleavage activity in vivo by determining whether inhibiting expression of the Chk1 gene would allow the G2/M checkpoint to be bypassed after DNA damage, as well as determining if the presence of **p53** influences the DNA-damage checkpoint response. The reagents were tested on asynchronous HeLa cells, to determine the extent of RNA and protein inhibition. To demonstrate whether cells bypass the G2/M checkpoint, HeLa cells (**p53**) were treated with etoposide to damage the DNA. Nocodazole and the potential checkpoint inhibitor were added 16 hours later, when all the cells should be arrested in G2. Nocodazole blocks cells from leaving mitosis, so if they have abrogated the checkpoint, the cells will be blocked in mitosis and appear rounded in shape. Eight GeneBloc reagents (sequences not provided in the specification) were selected against the Chk1 cDNA target. RNA inhibition

was measured after delivery of these reagents by GSG lipid to HeLa cells. Relative amounts of target RNA were measured versus actin using real time PCR monitoring amplification. Results showed that the GeneBloc reagents were effective in inhibiting Chk1 RNA in comparison to the controls. Protein levels assessed after 8, 24 and 32 hours after nucleic acid administration showed that the target protein was significantly reduced (80-90%) by 24 hours and remained low till day 5. Application of nucleic acid inhibitors in the checkpoint abrogation assay resulted in rounding up phenotype for the Chk1 target. Also there was an increase in Myt1 phosphorylation and large increase in PP1 phosphorylation. These results demonstrate that inhibitors of Chk1 activity can be used for treating certain types of cancer.

USE - (I) is useful for treating colorectal, lung, breast or prostate cancer, optionally in conjunction with one or more other therapies such as radiation and chemotherapy. Preferably, for cancer treatment, an antisense nucleic acid molecule is administered to the patient. (I) is useful for reducing Chk1 activity in the cell. (I) is useful for treating a patient having a condition associated with Chk1 level, which further involves use of one or more therapies suitable for the treatment. (I) is also useful for cleaving RNA of Chk1 gene. The cleavage is carried out in the presence of a divalent cation such as Mg2+ (claimed). Chk1 inhibition may be used in the therapeutic target for abrogating G2 DNA damage checkpoint arrest; a situation that selectively sensitizes **p53**-deficient tumor cell to radiation or chemotherapy treatment. (I) is also used for diagnosing diseases associated with Chk1 levels. (I) can also be used as diagnostic tools to examine genetic drift and mutations within diseased cells or to detect the presence of Chk1 RNA in a cell. The close relationship between ribozyme activity and the structure of the target RNA allows the detection of mutations in any region of the molecule which alters the base-pairing and the three-dimensional structure of the target RNA. By using multiple ribozymes nucleotide changes can be mapped which were important to RNA structure and function in vitro, as well as in cells and tissues. Cleavage of target RNAs with ribozymes can be used to inhibit gene expression and define the role of specified gene products in the progression of disease. The ribozymes are useful in detection of the presence of mRNAs associated with Chk1-related condition.

ADVANTAGE - The nucleic acid based molecules lead to better treatment of disease progression by affording the possibility of combination therapies.

Dwg.0/13

FS CPI

FA AB; DCN

MC CPI: B04-E01; B04-E06; B04-E08; B04-F0200E; B11-C08; B11-C08E5; B12-K04; B12-K04E; B12-K04F; B14-S03; D05-C07; D05-H12D2; D05-H12D5; D05-H12E; D05-H14B2; D05-H18

TECH UPTX: 20010924

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) is chemically synthesized (claimed).

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Nucleic Acid: (I) is an enzymatic nucleic acid molecule which comprises sequences complementary to any one of fully defined 1422 (S1-S1422) oligonucleotide sequences as given in specification such as CGGACAGUCCGCCGAGG (S1), GAGGUGCUCGGUGGAGU (S2), GGUGGAGUCAUGGCAGU (S3). The enzymatic nucleic acid molecule is in hammerhead (HH) motif which comprises sequences complementary to any one of fully defined 358 (S1)-(S358) oligonucleotide sequences as given in the specification; a hairpin; hepatitis Delta virus; group I intron; VS nucleic acid; amberzyme which comprises sequences complementary to any one of 631 (S791-S1422) substrate sequences as given in specification, such as GCCGGACAGUCCGCCGA, GACAGUCCGCCGAGGUG, CCGCCGAGGUGCUCGGU (S791-S793), etc; zinzyme which comprises sequences complementary to any one of 163 (S791-S954) substrate sequences as given in specification; or RNAse P nucleic acid motif; or NCH motif which comprises sequences complementary to any one of 321 (S359-S680) oligonucleotide sequences as given in the

specification, such as GGCCGGACAGUCCGCCG, GGACAGUCCGCCGAGGU, CAGUCCGCCGAGGUGCU (S359-S361), etc; or G-cleaver motif which comprises sequences complementary to any one of 109 (S681-S790) oligonucleotide sequences as given in the specification, such as GACAGUCCGCCGAGGUG, AGUCCGCCGAGGUGCUC, GCCGAGGUGCUCGGUGG (S681-S683), etc. The enzymatic nucleic acid molecules comprises 12-100 (preferably 14-24) bases complementary to the RNA of Chk1 gene. The enzymatic nucleic acid molecule comprises five ribose residues, at least 10 2'-O-methyl modifications and a 3' end modification (3'-3' inverted abasic moiety), phosphorothioate linkages on at least 3 of the 5' terminal nucleotides. Alternately, the enzymatic nucleic acid molecule is a DNAzyme which comprises sequences complementary to any one of 394 (S791-S1185) substrate sequences as given in specification. The DNAzyme comprises 10 2'-O-methyl modifications and a 3' end modification (3'-3' inverted abasic moiety), phosphorothioate linkages on at least 3 of the 5' terminal nucleotides. The nucleic acid molecule is an antisense nucleic acid molecule. The antisense nucleic acid molecule comprises five ribose residues, at least 10 2'-O-methyl modifications and a 3' end modification (3'-3' inverted abasic moiety), phosphorothioate linkages on at least 3 of the 5' terminal nucleotides. Sequence listing of antisense nucleic acid molecules not provided in the specification. (I) comprises a 2' sugar modification, nucleic acid base modification or phosphate backbone modification. (I) comprises a cap structure in the 5'-end and/or 3'-end. Preferred Mammalian Cell: (IV) is a human cell.

Preferred Expression Vector: (III) comprises an enzymatic or antisense nucleic acid molecule complementary to RNA of Chk1 gene. The vector comprises sequences encoding at least two of (I) which may be same or different and further comprises antisense or enzymatic nucleic acid molecule complementary to RNA of Chk1 gene.

ABEX UPTX: 20010924

SPECIFIC SEQUENCES - (I), an enzymatic nucleic acid molecule comprises any one of fully defined 1749 nucleic acid sequences (S1423)-(S3172) as given in the specification such as CCUCGGCGCUGAUGAGGCCGUUAGGCCGAAACUGUCCG, ACUCCACCCUGAUGAGGCCGUUAGGCCGAAAGCACCUC, ACUGCCAUCUGAUGAGGCCGUUAGGCCGAAACUC CACC, etc (claimed).

ADMINISTRATION - The nucleic acid molecules can be locally administered to relevant tissues ex vivo or in vivo through injection, infusion pump or stent, etc. The delivery of ribozyme or antisense expressing vectors can be systemic such as by intravenous or intramuscular route. Dosages range from 0.1-100 mg/kg body weight/day.

EXAMPLE - The sequence of human **checkpoint kinase** (Chk)-1 was **screened** for accessible sites using a computer-folding algorithm. Regions of the RNA were **identified** that did not form secondary folding structures. These regions contained potential ribozyme and/or antisense binding/cleavage sites. The sequences of these binding/cleavage sites comprise any one of fully defined 1422 (S1-S1422) oligonucleotide sequences as given in specification such as CGGACAGUCCGCCGAGG (S1), GAGGUGCUCGGUGGAGU (S2), GGUGGAGUCAUGGCAGU (S3). Ribozyme target sites were chosen by analyzing sequences of human Chk1 (Genbank accession number: AF016582) and prioritizing the sites on the basis of folding. Ribozymes were designated that could bind each target and were individually analyzed by computer folding to access whether the ribozyme sequences fold into the appropriate secondary structure. Those ribozymes with unfavorable intramolecular interactions between the binding arms and the catalytic core were eliminated from consideration. Ribozymes and antisense constructs were designed to anneal to various sites in the RNA message. The binding arms of the ribozymes were complementary to the target site sequences described above, while the antisense constructs were fully complementary to the target site sequences described above. The ribozymes and antisense constructs were chemically synthesized. The chemically synthesized ribozymes comprise any one of fully defined 1749 nucleic acid sequences (S1423)-(S3172) as given in the specification such

as CCUCGGCGCUGAUGAGGCCGUUAGGCCGAAACUGUCCG, ACUCCACCCUGAUGAGGCCGUUAGGCCGAAA GCACCUC, ACUGCCAUCUGAUGAGGCCGUUAGGCCGAAACUCCACC.

L84 ANSWER 6 OF 12 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-032064 [04] WPIX
DNN N2001-025019 DNC C2001-009878
TI Assaying phosphorylation enzyme activity on peptide immunologically with antibody to recognize phosphorylated state, useful in **screening** compounds to control enzyme activities e.g. signal transduction.
DC B04 D16 S03
IN KOBAYASHI, T; OGAWA, A; TAMAI, K; YANO, M
PA (IGAK-N) IGAKU SEIBUTSUGAKU KENKYUSHO KK; (MEDI-N) MEDICAL & BIOLOGICAL LAB CO LTD
CYC 21
PI WO 2000072011 A1 20001130 (200104)* JA 65p G01N033-53
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: US
JP 2000325086 A 20001128 (200110) 22p C12N015-09
EP 1184665 A1 20020306 (200224) EN G01N033-53
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 2000072011 A1 WO 2000-JP3193 20000518; JP 2000325086 A JP 1999-141187 19990521; EP 1184665 A1 EP 2000-929789 20000518, WO 2000-JP3193 20000518
FDT EP 1184665 A1 Based on WO 2000072011
PRAI JP 1999-141187 19990521
IC ICM C12N015-09; G01N033-53
ICS C07K016-40; C12N009-12; C12N015-54; C12Q001-48; G01N033-573
AB WO 200072011 A UPAB: 20010118
NOVELTY - A method for assaying protein phosphorylation enzyme activity in a sample with DNA-dependent **protein kinase**, **ATM** or/and ATR as the enzyme for phosphorylation, is new.

DETAILED DESCRIPTION - A method for assaying protein phosphorylation enzyme activity in a sample with DNA-dependent **protein kinase**, **ATM** or/and ATR as the enzyme for phosphorylation comprises:

(a) contacting a substrate peptide as sample with the enzyme for phosphorylation; and

(b) detecting the level of phosphorylation of the substrate peptide with an antibody that can recognize its phosphorylated state to evaluate the change in reactivity.

INDEPENDENT CLAIMS are also included for the following:

(1) a method for **screening** inhibitors or promoters of the protein phosphorylation enzyme activity comprising:

(a) incubation of the enzyme, substrate peptide and a test compound;

(b) detecting the level of phosphorylation with an antibody; and

(c) comparing the increase or decrease in phosphorylation with that of a control to select the compound;

(2) a method for assaying dephosphorylation enzyme activity of a protein in a sample as for the phosphorylation assay;

(3) a method for **screening** inhibitors or promoters of dephosphorylation enzyme activity of a protein carried out in a similar fashion as in (1);

(4) an assay of DNA-dependent protein kinase activity comprising:

(a) determination of the phosphorylation enzyme activity in the absence of a double-stranded DNA;

(b) similar determination in presence of the DNA; and

(c) comparing (a) and (b) to evaluate phosphorylation enzyme activity originated from the DNA-dependent protein kinase;

(5) compounds that can regulate the protein phosphorylation enzyme activity thus **screened** by any of the methods;

(6) an antibody that can recognize the phosphorylated state of a substrate peptide; and

(7) an assay kit containing the antibody.

USE - The assay is useful for evaluating the ability of an enzyme to

phosphorylate a peptide, which is useful in **screening** compounds to control enzyme activities e.g. signal transduction.
ADVANTAGE - The method is quick and convenient.
DESCRIPTION OF DRAWING(S) - The figure shows the control of cell cycle by DNA damage checkpoint.
Dwg.1/7

FS CPI EPI
FA AB; GI; DCN
MC CPI: B04-C01C; B04-G01; B04-L04; B11-C08; B11-C08E3; D05-A02B; D05-H09; D05-H11
EPI: S03-E14H4

TECH UPTX: 20010118
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: The substrate peptide has an amino acid sequence constituting an SQ motif or SQE motif. The antibody can recognize the phosphorylation site and can determine the individual activities of phosphorylation enzymes in a sample when a number of the enzymes present to phosphorylate at different sites. The phosphorylation enzyme is particularly ATM or ATR and the antibody can recognize the phosphorylated state of the SQE motif containing a serine residue at position 15 of **p53**, or is a DNA-dependent protein kinase with the antibody that can recognize the phosphorylated state of the SQ motif containing a serine residue at position 37 of **p53**. The substrate peptide is particularly a natural product. The antibody has high reactivity towards the phosphorylated or non-phosphorylated substrate peptide. Such substrate peptide can be labeled or immobilized. The antibody can be labeled. The evaluation of phosphorylation level is particularly by ELISA.

ABEX UPTX: 20010118
EXAMPLE - Six peptides with fully defined 14 amino acid sequences (given in the specification) were prepared with a synthesizer, containing amino acids of human **p53** with serine residues at positions 15, 33 or/and 37 as phosphorylation sites, which were linked to a carrier protein as antigens for producing antibodies. These substrate peptides and antibodies were then used in immunoassay of protein phosphorylation enzyme activity and in drug **screening.**

L84 ANSWER 7 OF 12 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2000-664872 [64] WPIX
DNN N2000-492792 DNC C2000-201339
TI Assays and screening methods based on direct interaction between FHA domains and phosphopeptides, useful for characterizing binding and to identify binding partners and modulators of FHA domain-phosphopeptide binding.
DC B04 D16 P14 S03
IN DUROCHER, D; **JACKSON, S P**
PA (KUDO-N) KUDOS PHARM LTD
CYC 93
PI WO 2000057184 A2 20000928 (200064)* EN 92p G01N033-566
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
GB 2348701 A 20001011 (200064) G01N033-68
AU 2000034407 A 20001009 (200103) G01N033-566
GB 2348701 B 20010620 (200136) G01N033-68
EP 1163521 A2 20011219 (200206) EN G01N033-566
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
ADT WO 2000057184 A2 WO 2000-GB1024 20000317; GB 2348701 A GB 2000-6533 20000317; AU 2000034407 A AU 2000-34407 20000317; GB 2348701 B GB 2000-6533 20000317; EP 1163521 A2 EP 2000-912756 20000317, WO 2000-GB1024

20000317
FDT AU 2000034407 A Based on WO 2000057184; EP 1163521 A2 Based on WO 2000057184
PRAI GB 1999-15075 19990628; GB 1999-6432 19990319
IC ICM G01N033-566; G01N033-68
ICS A01K067-00; A61K038-00; C07K005-00; C07K007-00; C07K007-04; C07K016-00; C07K019-00; C12N005-00; C12N015-00; G01N033-569
AB WO 200057184 A UPAB: 20001209
NOVELTY - Assays and screening methods based on a direct interaction between FHA domains and phosphorylated polypeptides, for characterizing binding between these molecules, the identification of binding partners, and for identifying substances which modulates the binding of an FHA domain to phosphopeptides.

DETAILED DESCRIPTION - Screening (M1) for a substance which modulates the binding of an FHA domain (I) to a phosphopeptide, comprises bringing (I) into contact with a phosphopeptide in the presence of one or more test substances and determining the binding of (I) to (II).

Screening or assay method (M2) for identifying (I) which binds to (II) of interest, or for determining the binding of (I) to (II) of interest, comprises bringing (I) into contact with (II) and determining the binding of the test (I) to (II).

Screening or assay method (M3) for identifying (II) which binds to an (I) or for determining the binding of (II) to (I), comprises bringing test (II) with (I) and determining the binding of the test (II) to the (I).

INDEPENDENT CLAIMS are also included for the following:

(1) (I) identified by (M2) which binds to a phosphorylated polypeptides comprising the amino acid sequence shown below;

(2) (II) identified by (M3) which binds to (I);

(3) an isolated nucleic acid molecule (III) encoding (I) or (II);

(4) a vector (IV) comprising (III);

(5) a host cell (V) comprising (IV);

(6) a transgenic animal comprising (V);

(7) preparation of (II) which involves expressing the nucleic acid encoding the unphosphorylated peptide and phosphorylating the expression product;

(8) a substance identified by (M1) as to be modulating the binding of (I) to a target (II);

(9) use of (I) in screening or searching for and/or obtaining or identifying, a (II) which binds to (I);

(10) use of (II) in screening or searching for, and/or obtaining or identifying, an FHA domain, which binds to (II);

(11) purifying a protein or polypeptide comprising (I) which is capable of binding (II), comprising contacting the material containing the polypeptide with a phosphopeptide;

(12) purifying (II), comprising contacting the material containing the (II) with a protein or polypeptide comprising (I);

(13) use of (II) for designing of a peptidyl or non-peptidyl mimetic of (II), which binds to (I) and/or modulates interaction between (I) and the (II);

(14) use of (I) for designing a peptide or non-peptidyl mimetic of an FHA1-like domain, which mimetic binds to (II);

(15) designing a mimetic of (II) which has biological activity of binding to (I) or a method of designing a mimetic of an (I) which has biological activity of binding to a target (II), involves analyzing a substance having the biological activity to determine the amino acid residues essential and important for the activity to define a pharmacophore, and modeling the pharmacophore to design and/or screen candidate mimetics having the biological activity;

(16) a mimetic obtained by the above method; and

(17) a pharmaceutical composition comprising one or more of (I), (II) or a substance identified by (M1).

-Thr(P)-X1-X2-Asp-

Thr(P) = a phosphorylated threonine residue; and

X1 and X2 = any amino acid residue.

ACTIVITY - Antimicrobial; cytostatic; antipsoriatic; ophthalmological; contraceptive; antiapoptotic; immunomodulator.

No supporting data is given.

MECHANISM OF ACTION - FHA domain-phosphopeptide interaction modulators; DNA repair; cell cycle control; gene therapy.

USE - The pharmaceutical composition comprising one or more of (I), (II) or a substance identified by (M1) is useful for preparing a medicament useful for treating a medical condition associated with a defect or disorder in transcriptional control, DNA replication, DNA repair, cell cycle control or other cellular process. It is also useful for treating a pathogen infection in an individual. (I) is used in screening or searching for and/or obtaining or identifying, a (II) which binds to (I). (I) is also used for designing a peptide or non-peptidyl mimetic of an FHA1-like domain, which binds to (II). (II) is used for screening or searching for, and/or obtaining or identifying, an FHA domain, which binds to (II). (II) is also used for designing of a peptidyl or non-peptidyl mimetic of (II), which mimetic binds to (I) and/or modulates interaction between (I) and the (II) (claimed).

The methods which modulate e.g. disrupt or interfere with the binding of an FHA domain to a phosphopeptide, to modulate any activity mediated by virtue of the binding, are useful for chemotherapy and/or radiotherapy, e.g. modulating interactions of FHA domain-containing proteins such as Chk2, NBS/Nibrin, Ki-67, and Dma1+ homologues, e.g. increasing the sensitivity of tumor cells to radiotherapy (chk2, NBS), e.g. treatment of p53-negative cancers by functional reactivation of checkpoint signaling, cancer cell apoptosis, cancer prophylaxis, treatment of other proliferative disorders e.g. psoriasis, cataracts (e.g. modulators of Ki-67 interaction, activators of checkpoint arrest), treatment of Ataxia-telangiectasia (A-T), Nijmegaen breakage syndrome (NBS) and other checkpoint deficiency diseases,contraception, anti-apoptosis, muscular (skeletal and cardiac) regeneration, immunomodulation, anti-bacterial activity, anti-viral activity, anti-fungal activity and plant biotechnology e.g. manipulating zeaxanthine epoxidase activity (zeaxanthine epoxidase is a key regulator of abscisic acid metabolism, abscisic acid is a phytohormone involved in seed dormancy and stress response). Quantifying the amount of (I) or (II) in a test sample may be used for diagnosis any of the above conditions or in the evaluation of a therapy to treat such a condition.

ADVANTAGE - The method provide valuable insights into checkpoint signaling, has important implications for the functions of other FHA domain-containing proteins, and provides basis for new lines of therapy.

Dwg.0/7

FS CPI EPI GMPI

FA AB; DCN

MC CPI: B04-B04C2; B04-B04L; B04-C01; B04-F09C; B04-G01; B04-N02A; B04-P0100E; B11-A; B11-C08E; B11-C09; B12-K04E; B14-A01; B14-A02; B14-A04; B14-C03; B14-G03; B14-H01B; B14-J01; B14-J05; B14-N01; B14-N03; B14-N17; B14-P01; D05-H07; D05-H09; D05-H10; D05-H11; D05-H18

EPI: S03-E14H4

TECH UPTX: 20001209

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred FHA domain: (I) comprises an amino acid sequence which shares 50% homology with the amino acids sequence of the FHA1 domain of Saccharomyces cerevisiae Rad53p.

Preferred Phosphopeptide: (II) binds to FHA1 domain of Rad53p and/or to Chk2.

Preferred Method: One or more of (II), (I) and the test substance is in a test sample. The method also involves quantifying the amount of (II), (I) or test substance in the sample. The method further involves purifying and/or isolating a test substance or and/or substance of interest from a mixture or extract. The method involves labeling one of (I) and (II) with the detectable label, immobilizing the other (I) and (II) on a solid

support and bringing the (I) and (II) into contact. The end-point of the assay is phosphorylation of Rad53p protein.
Preferred Modulators: The modulator identified by (M1) is an antibody, single chain antibody or its fragment directed to the site of binding in either (I) or (II) which are positions corresponding to arg-70 and his-88, of Rad53p. The antibody or single chain antibody is preferably directed at the motif -Thr(P)-X1-X2-Asp-.

ABEX UPTX: 20001209

WIDER DISCLOSURE - The following are also disclosed:
(1) unphosphorylated peptides and nucleic acid molecules encoding them;
(2) variant phosphopeptides; and
(3) derivatives the phosphopeptides.

SPECIFIC SEQUENCES - (II) comprises an amino acid sequence selected from (claimed):
APPLSQETFSDLWKL (ST)
APPLS(P)QETFSDLWKL (S(P)T)
APPLSQET(P)FSDLWKL (ST(P))
APPLSAET(P)FSDLWKL (ST(P)-2A)
APPLASQET(P)FSDLWKL (ST(P)-3A)
APPLSQAT(P)FSDLWKL (ST(P)-1A)
APPLSQET(P)ASDLWKL (ST(P)+1A)
APPLSQET(P)FADLWKL (ST(P)+2A)
APPLSQET(P)FSALWKL (ST(P)+3A)
ALAAAT(P)AADAAL (ST(P)5A)
ALAAADAADAAL (SD5A)
APPLSQES(P)FSDLWKL (SS(P))
GGKKATQSQEY (H2AS)
GGKKATQS(P)QEY (H2AS(P))
EXAMPLE - To test whether Rad9p can bind to the FHA1 domain of Rad53, cultures or from cultures of Saccharomyces cerevisiae carrying a deleted allele of RAD9 (rad9DELTA) were prepared prior to or after MMS treatment. Rad9p content was analyzed by SDS (sodium dodecyl sulfate)-gel electrophoresis followed by western blotting detection of Rad9p with anti-Rad9p polyclonal antiserum.
No rad9DELTA mutant was detected in the lane extract from the rad9DELTA mutant yeast, but Rad9p was detected in the extracts from wild-type yeast with and without MMS treatment, therefore demonstrating the specificity of the anti-Rad9p antiserum. Low and high mobility complexes of Rad9p were observed in the extract of wild-type yeast prior to MMS treatment. The low mobility forms detected after MMS treatment correspond to phosphorylated forms of Rad9, they are abolished after lambda protein phosphatase treatment but remained in extracts treated with both the lambda protein phosphatase and orthovanadate, an inhibitor of that phosphatase.
These interaction studies revealed that the FHA1 domain of Rad53 is able to bind Rad9p in the yeast extract. The FHA2 fusion protein is also able to bind Rad9p. In each case, the binding of Rad9p is stimulated dramatically by MMS and by 4-NQO. In marked contrast, the FHA1 R70A mutant fusion protein or GST alone do not bind Rad9p significantly.
Results revealed that only the phosphorylated forms of Rad9p that were induced upon genotoxic insult are efficiently retrieved from yeast extracts by FAH1 or FAH2. Furthermore, mutation of a conserved residue in FHA1, which results in impaired function in vivo, prevents the Rad9p interaction, providing indication that interaction between phosphorylated Rad9p and FHA1 is required for Rad53p biological function. The ability of the FHA1 (H88A), FHA1 (E117A) and FHA2 (R605A) mutants to bind phosphorylated Rad9p was tested.
A GST fusion of FHA1 (E117A) efficiently retrieved Rad9p from yeast extracts, whereas GST fusions of FHA1 (H88A) or FHA2 (R605A) did not. Thus the ability of Rad53p FHA domains to bind Rad9p correlates with their ability to function in checkpoint signaling. The inventions analyzed whether FHA1 can bind directly to ST(P) or any of the other phosphopeptides employed. A pulldown assay was employed in which

biotinylated peptides (5 ng), and bound protein was retrieved using streptavidin, coupled paramagnetic beads. After washing the beads extensively, the GST fusion proteins were then eluted, electrophoresed on an SDS polycrylamide gel and detected by western blotting using an anti-GST monoclonal antibody. Only the ST(P) peptide by not the unphosphorylated peptide (ST) nor the S(P)T phosphopeptide was able to specifically retrieve the GST-FHA1 protein. This pattern of phosphopeptide binding is therefore identical to the pattern observed in the competition experiments, and provided strong support for the notion that FHA1 binds Rad9p via the direct recognition of a Rad9p phospho-epitope.
To investigate the nature of the interaction between FHA1 and the ST(P) phosphopeptide, the effect of substituting residues surrounding the phosphothreonine with alanine and of substituting the phosphothreonine by phosphoserine was tested. Using the biotinylated-peptide pull-down assay described above, it was observed that alanine substitution of residues -3, -2, -1, +1 or +2 (relative to phosphothreonine) does not have a pronounced affect on interaction with GST-FHA1. However, substitution of the Asp residue at +3 by Ala ST(P)+3A was found to markedly decrease FHA1 binding, indicating that the +3 position is a major determinant of the binding specificity. Consistent with this, a penta-substituted peptide, T(P)5A, which retains the phosphothreonine and the Asp at +3, is still to bind FHAi effectively, and this interaction required a phosphothreonine since its substitution with the acidic amino acid Asp (D5A) abolished the penta-substituted peptide-FHA1 interaction, this interaction was still disrupted by the FHA1 mutations R70A or H88A.
Substitution of the threonine-phosphate in the original peptide for a serine-phosphate, yielding peptide SS(P), also reduced FHA1 binding to background levels. This implied that the binding of FHA1 was substantially specific for phosphothreonine residues. The above data established a consensus sequence for phosphopeptides which have the biological ability of binding to the FHA1 domain, i.e. the sequence - Thr(P)-X1-X2-Asp- wherein Thr(P) represents phosphorylated threonine and X1 and X2 each represent any amino acid.

L84 ANSWER 8 OF 12 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2000-558218 [51] WPIX
DNC C2000-166204
TI **Identifying** proteins with **ataxia telangiectasia**-mutated kinase substrate recognition sequences, useful for investigating **ATM kinase** specificity and treating human T cell leukemia virus.
DC B04 D16
IN CANMAN, C; KASTAN, M; KIM, S; LIM, D
PA (SJUD-N) ST JUDE CHILDREN'S RES HOSPITAL; (UYJO) UNIV JOHNS HOPKINS
CYC 89
PI WO 2000047760 A2 20000817 (200051)* EN 105p C12Q001-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000038570 A 20000829 (200062) C12Q001-00
US 6348311 B1 20020219 (200221) C12Q001-70
US 6387640 B1 20020514 (200239) C12Q001-48
US 2003022263 A1 20030130 (200311) C12Q001-48
ADT WO 2000047760 A2 WO 2000-US3386 20000209; AU 2000038570 A AU 2000-38570 20000209; US 6348311 B1 Cont of US 1999-248061 19990210, US 1999-400653 19990921; US 6387640 B1 US 1999-248061 19990210; US 2003022263 A1 CIP of US 1999-248061 19990210, Div ex US 1999-400653 19990921, US 2001-24123 20011217
FDT AU 2000038570 A Based on WO 2000047760
PRAI US 1999-400653 19990921; US 1999-248061 19990210; US 2001-24123

20011217
IC ICM C12Q001-00; C12Q001-48; C12Q001-70
ICS C12N001-20; C12N005-00; C12N009-12; C12N015-00
AB WO 200047760 A UPAB: 20001016
NOVELTY - **Identifying** an **ataxia telangiectasia** -mutated (**ATM**) **kinase** substrate recognition sequence in a protein comprising contacting an **ATM kinase** with a fusion peptide containing a structural portion and a candidate **ATM kinase** where the fusion protein does not contain a sequence of 14 amino acids (aa; I), given in the specification, is new.

DETAILED DESCRIPTION - **Identifying** an **ataxia telangiectasia**-mutated (**ATM**) **kinase** substrate recognition sequence in a protein comprising contacting an **ATM kinase** with a fusion peptide containing a structural portion and a candidate **ATM kinase** where the fusion protein does not contain a sequence of 14 amino acids (aa; I), given in the specification, is new.

Ser-Val-Glu-Pro-Pro-Leu-Ser-Gln-Glu-Thr-Phe-Ser-Asp-Leu (I)

INDEPENDENT CLAIMS are also included for the following:

(1) **identifying** a putative **ATM kinase** target protein comprising analyzing the sequence of a protein to determine whether it contains a sequence corresponding to the 7 residue consensus sequence (II), given in the specification;

(2) **identifying** an ATM-regulated process comprising:

(a) modulating ATM-mediated phosphorylation of a target protein comprising an ATM substrate recognition sequence as in (II); and

(b) determining whether modulation of ATM-mediated phosphorylation of the target protein affects a pathway;

(3) modulating an ATM-regulated process comprising modulating ATM-mediated phosphorylation of a target protein comprising an **ATM kinase** substrate recognition sequence in a cell, where the protein is not **p53**;

(4) a nucleic acid encoding a kinase dead ATM mutant where the resulting protein any number of positions including 1 of Asp2870 and Asn2875;

(5) a recombinant vector which codes for expression defective ATM polypeptide;

(6) a recombinant cell containing the vector of (5);

(7) a recombinant vector encoding a fusion protein containing a structural portion and an **ATM kinase** recognition sequence where the protein does not contain (I);

(8) **screening** for a compound that modulates ATM-mediated phosphorylation comprising detecting a change in the level of ATM-mediated phosphorylation of a peptide comprising an ATM substrate recognition sequence in the presence of a control compound;

(9) **screening** for compounds that induce an ATM-regulated pathway in a cell, comprising contacting the cell with a candidate compound and detecting whether the ATM-mediated process is induced in the cell, where the cell is defective for the expression of ATM and the pathway is not a tumor suppression or cell cycle control pathway;

(10) composition comprising ATM and a polypeptide where the polypeptide comprises an **ATM kinase** substrate recognition sequence and does not contain (I);

(11) a peptide comprising a sequence corresponding to an ATM substrate recognition consensus sequence motif as in (II), but not the sequence of (I);

(12) **identifying** a modulator of ATM-mediated activity comprising determining the extent of human T cell leukemia virus (HTLV) integration in the presence of the potential modulator; and

(13) inhibiting HTLV integration comprising contacting a cell with an ATM inhibitor.

B1-X-B2-S-Q-X-X (II)

X = any aa;

B1 = any hydrophobic aa; and
B2 = any hydrophobic aa or D.
ACTIVITY - Cytostatic; cardiant; vasotropic; anorectic; antiviral; anti-HIV.
MECHANISM OF ACTION - **Ataxia telangiectasia** -mutated (**ATM**) **kinase** modulation.
USE - The methods are useful for investigating **ATM kinase** specificity and to **identify** ATM target proteins other than **p53.** The modulation of ATM activity may be used to treat cancer (e.g. to radiosensitize tumors), cardiovascular disease (e.g. restenosis), revascularization, obesity and retroviral infections (e.g. HIV and especially human T cell leukemia virus (HTLV; claimed)), Dwg.0/4

FS CPI
FA AB; DCN
MC CPI: B04-C01B; B04-C01C; B04-E02B; B04-E02F; B04-E08; B04-F0100E; B04-H01; B04-M01; B04-N02B; B11-C08E; B11-C08E2; B12-K04E; B14-A02B1; B14-E12; B14-F01; B14-F02D; B14-H01B; D05-H09; D05-H12B; D05-H12C; D05-H12E; D05-H14; D05-H17C
TECH UPTX: 20001016
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Fusion Protein: The structural portion of the fusion protein lacks ATM recognition sequences. The candidate sequence has an **ATM kinase** recognition sequence including a phosphorylatable serine. The candidate sequence has a modified **ATM kinase** recognition sequence that lacks an amino acid residue phosphorylatable by **ATM kinase.** The structural protein is preferably GST. The candidate peptide comprises 1 of 12 sequences ((III)-(XIV)) of 13 or 14 aa given in the specification.
Preferred Recognition Motif: The ATM substrate recognition motif comprises 1 of 2 sequences of 7 residues ((XV) and (XVI)).
Preferred Target Protein: The target protein is involved in double stranded DNA break repair, telomere synthesis or repair, the aging process, tumor suppression, insulin or insulin-like growth factor (IGF)-I signaling, cell cycle control, affecting cell survival after HTLV infection and autophosphorylation. The target protein is preferably NBS/p95, MRE11, PHASI, CHK1, Werner, PST1, CUT1, ATM1, BRCA1 and RAD17.
Preferred Methods: The method of (2) further comprises determining whether the sequence corresponding to an ATM substrate recognition consensus sequence is phosphorylated by ATM, preferably by contacting **ATM kinase** with a fusion peptide containing a structural protein and an ATM substrate recognition consensus sequence, and detecting whether the fusion peptide is phosphorylated. The method optionally comprises determining whether the ATM substrate recognition consensus is phosphorylated by ATM comprising contacting **ATM kinase** with the target protein and detecting phosphorylation. In the method of (4), ATM-mediated phosphorylation is inhibited by expressing a kinase dead ATM mutant in the cell, alternatively increasing ATM-mediated phosphorylation comprises by increasing the level of expression of ATM in a cell. The ATM-regulated process is affecting cell survival after HTLV infection or is IGF-I signaling. In the method of (8) the compound selectively modulates ATM-mediated phosphorylation. The method further comprises detecting the inhibition of a cellular process mediated by ATM phosphorylation of a target protein. The change of a cellular process is the loss of S-phase checkpoint, a defect in the G2/M checkpoint, an increase in radiosensitivity, and an increase in sensitivity to chemotherapeutic agents. In the method of (9), **screening** comprises contacting a cell line that expresses a kinase dead mutant with a candidate compound and testing for ATM-mediated pathway induction.
E.g.:
Thr-Pro-Gly-Pro-Ser-Leu-Ser-Gln-Gly-Val-Ser-Val-Asp-Glu (III);
Glu-Pro-Pro-Met-Glu-Ala-Ser-Gln-Ser-His-Ile-Arg-Asn-Ser (V);
Lys-Ala-Tyr-Ser-Ser-Ser-Gln-Pro-Val-Ile-Ser-Ala-Gln (VII);
Trp-Glu-Thr-Pro-Asp-Leu-Ser-Gln-Ala-Glu-Ile-Glu-Gln (IX);

Pro-Leu-Leu-Met-Ile-Leu-Ser-Gln-Leu-Leu-Pro-Gln-Gln-Arg (XI);
Thr-Trp-Ser-Leu-Pro-Leu-Ser-Gln-Asp-Ser-Ala-Ser-Glu-Leu (XIII);
Pro-Pro-Asp-Ser-Gln-Glu-Xaa (XV); and
Leu-Pro-(Leu/Ala)-Ser-Gln-(Asp/Pro)-Xaa.
Xaa = any aa.

ABEX UPTX: 20001016

EXAMPLE - The full-length cDNA encoding NH2-terminal, FLAG-tagged wild-type **ataxia telangiectasia**-mutated (**ATM**) **kinase** was excised from pFB-YZ3 and subcloned into the XhoI site of pcDNA3 to generate pcDNA-FLAG-ATMwt. Catalytically inactive ATM was generated by mutating a cDNA fragment encoding the PI3 kinase-related domain of ATM by overlap PCR substituting Asp2870 with Ala and Asn2875 with Lys. The fragment encoding the kinase domain was excised from wild type ATM and replaced with a BpuI 101 I-XhoI fragment to generate pcDNA-FLAG-ATMkd. Cells (293T) were transiently transfected with 10 micro g of either pcDNA-FLAG-ATMwt, pcDNA-FLAG-ATMkd, pBJF-FRPwt or pBJF-FRPkd using calcium phosphate and harvested 2 days later. Cells were lysed through sonication and centrifuged at 13000 x g. Extract (2 mg) was incubated with mouse IgG and protein A/G sepharose beads. FLAG-tagged proteins were then immunoprecipitated with anti-FLAG M2 monoclonal antibody and protein A/G sepharose beads. Immunoprecipitants were washed twice with kinase buffer (10 mM Hepes (pH 7.5), 50 mM glycerophosphate, 50 mM NaCl, 10 mM MgCl2, 10 mM MnCl2, 5 micro M ATP, and 1 mM DTT). Kinase reactions were initiated by resuspending washed beads in 30 micro l of kinase buffer containing 10 micro Ci (gamma-32P) ATP and 1 micro g glutathione S-transferase-conjugated (GST)p531-101 and incubated for 30 minutes at 30 degreesC. Proteins were electrophoretically separated, transferred to nitrocellulose and analyzed on a PhosphorImager (RTM). Although the proteins could be detected with an anti-FLAG or anti-**p53** antibody, only wild type enzyme was found to phosphorylate GSTp531-101. ATM did not phosphorylate GST alone.

L84 ANSWER 9 OF 12 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1999-405032 [34] WPIX
DNN N1999-301912 DNC C1999-119542
TI New isolated mammalian nucleic acid encoding Rad1.
DC B04 D16 J04 S03
IN FREIRE, R; **JACKSON, S P**
PA (CANC-N) CANCER RES CAMPAIGN TECHNOLOGY; (KUDO-N) KUDOS PHARM LTD
CYC 85
PI WO 9931234 A1 19990624 (199934)* EN 96p C12N015-12
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
GB 2333776 A 19990804 (199934) C07K014-47
AU 9915721 A 19990705 (199948)
GB 2333776 B 20000524 (200028) C07K014-47
EP 1037978 A1 20000927 (200048) EN C12N015-12
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 2002508180 W 20020319 (200222) 73p C12N015-09
ADT WO 9931234 A1 WO 1998-GB3782 19981216; GB 2333776 A GB 1998-27704 19981216; AU 9915721 A AU 1999-15721 19981216; GB 2333776 B GB 1998-27704 19981216; EP 1037978 A1 EP 1998-960037 19981216, WO 1998-GB3782 19981216; JP 2002508180 W WO 1998-GB3782 19981216, JP 2000-539134 19981216
FDT AU 9915721 A Based on WO 9931234; EP 1037978 A1 Based on WO 9931234; JP 2002508180 W Based on WO 9931234
PRAI GB 1997-26575 19971216
IC ICM C07K014-47; C12N015-09; C12N015-12
ICS A61K038-17; C12N001-15; C12N001-19; C12N001-21; C12N005-10; C12P021-02; C12Q001-68; G01N033-15; G01N033-50; G01N033-566

ICA A61P035-00; C07K016-18
AB WO 9931234 A UPAB: 19990825
NOVELTY - Human and mouse homologs of the Schizosaccharomyces pombe Rad1 gene, are new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a novel isolated mammalian Rad1 polypeptide selected from:
(a) a human polypeptide having an amino acid sequence (I) shown (human Rad1 (hRad1), 282 amino acids in length);
(b) the mouse polypeptide having an amino acid sequence (II) (mouse Rad1 (mRad1), 280 amino acids in length); and
(c) alleles of (a) or (b).
(2) an isolated polypeptide which has an amino acid sequence which shares at least 80% identity with (I);
(3) an isolated fragment of (I) which is at least 5 amino acids in length;
(4) an assay for obtaining an agent able to interact with a polypeptide or fragment as defined above, comprises:
(a) bringing into contact a substance which includes a polypeptide or fragment, and a test compound; and
(b) determining interaction between the substance and the test compound;
(5) an assay for obtaining an agent able to modulate interaction between hRad1 and proliferating cell nuclear antigen (PCNA), comprises:
(a) bringing into contact a substance which includes a polypeptide of (II) or a fragment, a substance including PCNA or its portion, able to interact with the polypeptide or fragment; and a test compound; and
(b) determining interaction between the substances;
(6) an assay for obtaining an agent able to affect hRad1 activity, comprises:
(a) bringing into contact a substance which includes a polypeptide of (1), and a test compound; and
(b) determining hRad1 activity;
(7) an isolated specific binding member comprising an antigen-binding domain of an antibody specific for a polypeptide as in (1);
(8) an isolated polynucleotide (PN) encoding a polypeptide as in (1) or (2);
(9) an isolated PN encoding a fragment as in (3);
(10) an expression vector comprising a PN as in (8) or (9) operably linked to regulatory sequences for expression of the polypeptide or fragment;
(11) a host cell transformed with an expression vector as in (10); and
(12) a method of making a polypeptide comprises culturing the host cell of (11); and
(13) a method of determining in a sample for the presence or absence of nucleic acid encoding the polypeptide of (1).
ACTIVITY - Anti-Hiv; Cytostatic; Antiarteriosclerotic; Antipsoriatic.
MECHANISM OF ACTION - None given.
USE - The Rad1 polypeptides are involved in DNA replication arrest and DNA damage-induced signaling pathways. They can be used for the development of novel diagnostic, prophylactic and therapeutic agents for diseases such as cancer, infertility and degenerative disease states that may be associated with loss of function of these polypeptides. The Rad1 polypeptides interact with PCNA and can be used to develop agents which modulate this interaction and thus cellular processes, e.g. for regulating immune system function, for treating **ataxia-telangiectasia** (A-T), for AIDS therapy, for **p53** therapy, to treat or prevent disease states associated with premature and normal aging, or for treating tumors, cancers, psoriasis, arteriosclerosis and other hyper-proliferative disorders.
Dwg.0/0
FS CPI EPI

FA AB; DCN
MC CPI: B04-E02F; B04-E08; B04-N02; B12-K04A1; B14-F07; B14-H01; B14-N17C; D05-H09; D05-H12A; D05-H12E; D05-H14; D05-H17A6; J04-B01
EPI: S03-E14H; S03-E14H4
TECH UPTX: 19990825
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Sequence: The fragment of (3) is less than 40 amino acids long. The fragment is able to interact with PCNA and/or inhibit interaction between hRad1 and PCNA.
Preferred Assay: The assay further includes determining the ability of the test compound or an agent obtained in the assay to affect hRad1 activity. The agent obtained is a peptide fragment of hRad1 or PCNA.
Isolation: The human and mouse homologs of the Schizosaccharomyces pombe Rad1 gene were isolated using standard recombination techniques.
ABEX UPTX: 19990825
EXAMPLE - A sequence of 484bp (GeneBank Acc. Number AA029300) was identified from a human uterus cDNA library in the expressed sequence tag (EST) database, whose predicted protein product displays a weak but significant homology (30% identity, 58% similarity - search done with the BLAST algorithm) to a region of 87 amino acid residues in the carboxyl-terminal portion of the S. pombe Rad1 protein. PCR was used with a human B-cell cDNA library, and a PCR product was generated. Cloning and sequencing of a variety of products revealed that some but not all contained overlapping clones of the same cDNA. Analysis of the putative product of this partial cDNA indicated that it displays homology with Schizosaccharomyces pombe Rad1 outside of the sequence initially identified as the EST. The full-length cDNA clone was obtained by PCR with primers that had been designed so that they would correspond to the 5' and 3' ends of the gene. Sequencing of this product verified that its translation product did indeed correspond to an apparently full-length homolog of S. pombe Rad1. PCR was also used to isolate mouse Rad1 cDNA.

L84 ANSWER 10 OF 12 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1999-357474 [30] WPIX
DNC C1999-105723
TI **Identifying** secondary gene targets lethal to tumor cells, used to **screen** for anticancer agents.
DC B01 B04 D16
IN FRIEND, S; HARTWELL, L
PA (HUTC-N) HUTCHINSON CANCER RES CENT FRED
CYC 81
PI WO 9924603 A1 19990520 (199930)* EN 41p C12Q001-02
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9913100 A 19990531 (199941)
EP 1029072 A1 20000823 (200041) EN C12Q001-02
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 2001521763 W 20011113 (200204) 54p C12Q001-68
US 2002064784 A1 20020530 (200240) C12Q001-68
AU 753469 B 20021017 (200280) C12Q001-02
ADT WO 9924603 A1 WO 1998-US23597 19981106; AU 9913100 A AU 1999-13100 19981106; EP 1029072 A1 EP 1998-956616 19981106, WO 1998-US23597 19981106; JP 2001521763 W WO 1998-US23597 19981106, JP 2000-519596 19981106; US 2002064784 A1 Provisional US 1997-64657P 19971106, Provisional US 1998-80471P 19980402, Cont of US 1998-187229 19981106, US 2001-847588 20010503; AU 753469 B AU 1999-13100 19981106
FDT AU 9913100 A Based on WO 9924603; EP 1029072 A1 Based on WO 9924603; JP 2001521763 W Based on WO 9924603; AU 753469 B Previous Publ. AU 9913100, Based on WO 9924603
PRAI US 1998-80471P 19980402; US 1997-64657P 19971106; US 1998-187229

19981106; US 2001-847588 20010503
IC ICM C12Q001-02; C12Q001-68
ICS A01N061-00; A61K045-00; A61P035-00; C12N015-09
AB WO 9924603 A UPAB: 19990802
NOVELTY - A secondary drug target (SDT) is **identified** by:
(i) introducing at least one mutation, at secondary sites, into the genome of a cell that already has at least one primary gene defect (PGD);
(ii) selecting a secondary site mutation (SSM) that is lethal to the cell and
(iii) determining the gene product of the lethal secondary site to provide SDT.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) method for rational antitumor drug design by:
(a) **identifying** a secondary target gene (STG) in an organism having an altered gene analogous or homologous to a primary tumor defect;
(b) **identifying** an analogous or homologous secondary target in a mammalian cell; and
(c) using this target to **screen** agents for antitumor activity;
(2) treating cancer with an agent (I) that interacts with, binds to or inhibits a gene product of an STG in a mammalian tumor cell; and
(3) composition that contains an agent (Ia):
(a) derived from the gene product of a lethal SSM, (Ia) being this product (or its active fragment, derivative or analog), or a small molecule or peptide mimetic; or
(b) able to inhibit expression of a synthetic lethal gene or the activity of its gene product.
ACTIVITY - Cytostatic.
MECHANISM OF ACTION - None given.
USE - SDT are used to **screen** for drugs and drug candidates which inhibit the growth of a human tumor.
ADVANTAGE - **Screening** based on SDT can produce drugs that are selective, even specific, for tumor cells (since normal cells lack the primary defect and the secondary defect is not, by itself, lethal). The method allows all gene products that, if mutated, are lethal to cells to be **identified**, i.e. the entire genome may be scanned to determined the best SDT.
Dwg.0/7
FS CPI
FA AB; DCN
MC CPI: B11-C08E4; B12-K04A1; D05-H09
TECH UPTX: 19990802
TECHNOLOGY FOCUS - BIOLOGY - Preferred Method: The PGD is present in, or associated with, a human tumor, or is analogous or homologous to such a defect, resulting in alteration, loss, inhibition, enhancement or gain of function, particularly suppression of tumor growth, DNA damage checkpoint, DNA mismatch repair, nucleotide excision repair, O6-methylguanine reversal, double-stranded break repair, DNA helicase, signaling, cell cycle control or apoptosis. The signaling function includes signal transduction, tissue growth factor signaling, autocrine loop signaling or paracrine loop signaling.
PGD are particularly present in any of about 50 specified genes, such as, p16, **p53**, ATM, MSH2, MLH1, XP-A, XP-B, MGMT, BRCA2, BRCAI, BLM, RAS, NF1, MYC, PTH, Cyclin D, Cyclin E, p27kip1, Rb, BCL-2, RAD9Sc, rad1+Sp, MEC1Sc, TEL1Sc, rad3+Sp, mei-41Dm, MSH2Sc, MLH1Sc, RAD14Sc, RAD25Sc, MGT1Sc, RAD51Sc, RAD54Sc, SGS1Sc, rqh1+Sp, dRASDm, RASCe, RAS1Sc, RAS2Sc, let-60Ce, IRAISc, IRA2Sc, dMycDm, patchedDm, CLN1Sc, CLN2Sc, Cyclin DDm, Cyclin EDm, SIC1Sc, RbfDm, or ced-9Ce, particularly yeast genes that encode CLN2 (a cyclin at the G1/S checkpoint) or a PIK-related kinase (from the yeast gene mec1).
The secondary mutation is introduced into:

(a) any of about 30 specified genes, such as, cdc9, cdc2, a gene encoding a gene product exhibiting polymerase 8 exonuclease function, a gene encoding a gene product exhibiting polymerase epsilon exonuclease function, a gene encoding a ribonucleotide reductase, mecl, rad53 like gene, cdc53, cdc34, cdc14, cdc15, a gene encoding NUP170, dbf2, a gene encoding CLN2, rad3, rad9, rad27, cdc8, a gene encoding Mlu1-box binding factor, slm 1, a gene encoding MBF, a gene encoding PCNA, or a gene encoding a replication fork protein, particularly, where the primary defect is in CLN2, those that encode PIK-related kinase (mec1), E2 ubiquitin carrier protein (cdc34), E3 ubiquitin ligase (cdc35), ubiquitin ligase (skp1),protein phosphatase (cdc14) or nuclear pore protein (NUP170); or
(b) into a gene having a mammalian analog or homolog, e.g. those expressing DNA ligase I, a DNA polymerase, ribonucleotide reductase, FEN-1, Cyclin D, Cyclin E, NUP155, isozyme, or an **ataxia telangiectasia**-related (ATR) gene.
The SDT **identified** is optionally used to **screen** for drugs, or drug candidates (preferably a small molecule), specifically those that interact with, bind to or inhibit products of the genes listed as secondary targets. The drug or drug candidate interacts with, binds to, or inhibits a gene product selected from DNA ligase, DNA polymerase, polymerase delta exonuclease, polymerase epsilon exonuclease, ribonucleotide reductase, a subunit of transcriptional activator, a transcription factor, PCNA, a replication fork protein, PIK-related kinase, recombinase, E3 ubiquitin ligase, E2 ubiquitin carrier protein, a protein tyrosine phosphatase, a nuclear pore protein, cyclin, DNA repair exonuclease, thymidylate kinase, gene product of sLm1, ribonucleotide reductase, or a transcriptional activator.
The method further comprises validating the synthetic lethality of the analogous or homologous secondary target in a mammalian tumor cell relative to a mammalian non-tumor cell. The secondary target gene is **identified** by performing a synthetic lethal **screen.** The SSM is effected within a gene selected from, RNRI, RNR2, RNR4, CDC8, CDC21, SHM2, PRII, CDC17, M13PI, SLM I, SLIA2, SLM3, and SLM4. The PGD includes a defect in a gene coding for PIK-related kinase (mecl), and the secondary site mutation is effected within a gene selected from RNRI, RNR2, RNR4, MCS, CDC21, SHM2, PRII, CDC17, NIBM, SLMI, SLM2, SLM3, and SILM4.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred compositions: The human gene comprises an AT-related gene. (Ia) inhibits the activity of ATR. (Ia) inhibits division, growth or viability of a cell having a PGD, but not a cell lacking this. Particularly the PGD results in abnormal accumulation of a human G1/S cyclin (either because of overexpression or reduced degradation), particularly cyclin D1 or E. The synthetic lethal gene product is particularly a human isozyme of cdc 34, 53 or 14; skp1; NUP155 or the **ATR protein kinase.**

ABEX UPTX: 19990802

EXAMPLE - In a typical **screening** process, a yeast strain is constructed to carry a wild-type copy of the gene (A) being analyzed, under control of the GAL1 promoter. The cells are mutated, e.g. with ultraviolet light, to 10-30% survival and colonies having a secondary mutation that, when taken in conjunction with a primary defect, is lethal are **identified** from ability to grow on galactose but not on dextrose. Selected colonies are transformed with a plasmid containing (A), resulting in cells able to grow on dextrose. These transformants are crossed with a wild-type strain of the opposite mating type and if the hybrids can grow on glucose this indicates that the synthetic lethal mutation is recessive and clonable by complementation.
If growth on glucose is not observed then the mutation is dominant and is not examined further. Hybrids carrying the recessive mutations are crossed with wild-type strains, sporulated and the spore tetrads analyzed for the appropriate single-mutation pattern of segregation for the lethal

phenotype. Mutants with the correct pattern are cloned by complementation.

L84 ANSWER 11 OF 12 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1995-263824 [34] WPIX
DNC C1995-120141
TI **p53** responsive element(s) for down-regulation of bcl-2 gene and up-regulation of bax gene - and **identification** of agent(s) useful to modulate cell death, e.g. cancer or stroke.
DC B04 D16
IN HANADA, M; HARIGAI, M; MIYASHITA, T; REED, J C
PA (LJOL-N) LA JOLLA CANCER RES FOUND; (BURN-N) BURNHAM INST
CYC 19
PI WO 9519367 A1 19950720 (199534)* EN 69p C07H017-00
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: CA JP
US 5484710 A 19960116 (199609) 18p C12P021-00
US 5659024 A 19970819 (199739) 28p C07H021-04
US 5908750 A 19990601 (199929) C12Q001-68
ADT WO 9519367 A1 WO 1995-US710 19950112; US 5484710 A US 1994-182619 19940114; US 5659024 A CIP of US 1994-182619 19940114, US 1994-330535 19941027; US 5908750 A CIP of US 1994-182619 19940114, Div ex US 1994-330535 19941027, US 1997-838844 19970411
FDT US 5659024 A CIP of US 5484710; US 5908750 A CIP of US 5484710, Div ex US 5659024
PRAI US 1994-330535 19941027; US 1994-182619 19940114; US 1997-838844 19970411
REP 6.Jnl.Ref; US 5362623
IC ICM C07H017-00; C07H021-04; C12P021-00; C12Q001-68
ICS C12N015-09; C12Q001-02
AB WO 9519367 A UPAB: 19950904
A nucleotide sequence (I) comprising a **p53**-responsive element (**p53**-RE) that binds **p53** and down-regulates the expression of a gene and a nucleotide sequence (II) comprising the bax promoter are new. Also claimed are: (1) **identification** methods for an agent (e.g. drugs) that effectively regulates (down- or up-regulation) the expression of a gene involved in apoptosis in a **p53**-deficient cell; and (2) an effective agent as **identified** in (1).
The **identification** of **p53**-RE-D and **p53** -RE-U allows manipulation of the mechanism by which cell death is regulated in diseases that are characterised by abnormal levels of cell death, e.g. cancer, stroke, Alzheimer's disease, **ataxia telangiectasia**, Bloom's syndrome and progeria. The **screening** assays provide a method for **identifying** an effective agent, which can be used to modulate cell death in a cell in vitro or in a patient. Agents that decrease the level of cell death are partic. useful for treating a patient having a disease characterised by abnormally high levels of apoptosis (claimed). The agents may also be used to reduce or prevent toxicity of a normal cell, esp a neuron or lymphocyte, in a patient receiving therapy, especially chemo- or radiotherapy. Administration may be intrathecal (e.g. to treat a neurodegenerative disorder or stroke) or i.v. (e.g. to treat cancer).
Dwg.0/11
FS CPI
FA AB
MC CPI: B04-E01; B11-C08E; B12-K04A; B14-H01; B14-J01A4; B14-N16; D05-H09; D05-H12D5
ABEQ US 5484710 A UPAB: 19960305
A method of down-regulating the expression of a gene, comprising operatively linking a **p53**-responsive element having the 190 bp sequence given in the specification or an active fragment thereof to the gene and expressing the gene.
Dwg.0/8
ABEQ US 5659024 A UPAB: 19970926

An isolated nucleotide sequence, comprising the bax promotor (972 bp sequence given in the specification), or a fragment which comprises a **P53** binding site and confers regulatory activity upon a gene, is new.
Dwg.0/11

L84 ANSWER 12 OF 12 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1993-336939 [42] WPIX
DNC C1993-149124
TI Detection of point mutations using mismatch repair enzymes - useful in diagnosis of some genetic disorders.
DC B04 D16
IN HSU, I; LU-CHANG, A
PA (UYMA-N) UNIV MARYLAND BALTIMORE
CYC 20
PI WO 9320233 A1 19931014 (199342)* EN 43p C12Q001-68
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA JP
AU 9339192 A 19931108 (199408) C12Q001-68
US 5683877 A 19971104 (199750) 11p C12Q001-68
ADT WO 9320233 A1 WO 1993-US2329 19930322; AU 9339192 A AU 1993-39192 19930322; US 5683877 A Cont of US 1992-859072 19920327, Cont of US 1994-309629 19940921, US 1995-465798 19950606
FDT AU 9339192 A Based on WO 9320233
PRAI US 1992-859072 19920327; US 1994-309629 19940921; US 1995-465798 19950606
REP 4.Jnl.Ref
IC ICM C12Q001-68
ICS C12P019-34
AB WO 9320233 A UPAB: 19931202
A new method for **identifying** a nucleotide base at a single site in a nucleic acid comprises (a) obtaining single stranded target nucleic acid sequences; (b) hybridising oligonucleotides comprising said site to said single stranded nucleic acid sequences wherein said oligonucleotides may or may not be complementary at said site in said single stranded nucleic acid sequences, to form oligonucleotide - target nucleic acid sequence hybrids; (c) exposing said nucleic acid sequence hybrids to an enzyme that binds to mismatch bases to form enzyme-nucleic acid complexes or that cleaves one strand containing a mismatched base pair to produce cleaved fragments; (d) determining the presence of said enzyme nucleic acid complexes or said cleaved fragments; and (e) **identifying** the nucleotide base at said site by virtue of whether a reaction with an oligonucleotide forms a complex or produces cleaved fragments.
USE/ADVANTAGE - The invention provides a sensitive and accurate method for detecting base pair mismatches in nucleic acid sequences and particularly in DNA sequences such as genomic DNA sequences. Another object of the invention is to provide a method for **identifying** the nucleotide at a specific site in a nucleic acid without using sequencing methods. The invention is useful in the diagnosis of genetic disorders that arise from point mutations in, e.g., Kinases, growth factors, receptor binding proteins and nuclear proteins. These disorders include cystic fibrosis, xeroderma pigmentusum, **ataxia telangiectasia**, Blooms' syndrome, the haemoglobinopathies such as thalassaemia and sickle cell disease; other diseases that arise from inborn errors of metabolism such as phenylketonuria, muscular dystrophy; mental retardation syndrome such as the fragile-X syndrome, Albright's osteodystrophy; specific genes associated with cancer such as DCC, NF-1, RB, **p53**, erbA, and the Wilm's tumour gene; and oncogenes such as ab1, erbB, src, sis, ras, fos, myb, myc.
Dwg.0/0
FS CPI
FA AB
MC CPI: B04-B02C4; B04-B04A1; B11-C08E3; B12-K04A; D05-H09; D05-H12

ABEQ US 5683877 A UPAB: 19971217

A method for **identifying** a nucleotide base pair at a point mutation site in a target double-stranded DNA molecule for which the corresponding wild-type DNA sequence has been determined, using a endonuclease that recognizes a base pair mismatch consisting of a first base and a second base, comprising:

(A) denaturing said target double-stranded DNA molecule comprising said point mutation site into a first single-stranded target DNA molecule and a second single-stranded target DNA molecule, wherein said first single-stranded target DNA molecule comprises a first DNA sequence and said second single-stranded target DNA molecule comprises a second DNA sequence complementary to said first DNA sequence;

(B) preparing a first, a second, a third and a fourth DNA probe, each comprising said mutation site, wherein said first and said second probes comprise said first DNA sequence, and said third and said fourth probes comprise said second DNA sequence, and wherein said first and said third probes contain at the mutation site said first base recognized by said mismatch endonuclease, and said second and said fourth probes contain at the mutation site said second base recognized by said mismatch endonuclease;

(C) hybridizing said first, second, third and fourth DNA probes with the resulting single-stranded target DNA molecules of step (A) to form DNA probe-target DNA hybrid molecules comprising said mutation site in individual reaction vessels in the following manner:

(1) said first DNA probe labelled with a detectable marker is hybridized to said second single-stranded target DNA molecule; (2) said second DNA probe is hybridized to said second single-stranded target DNA molecule labelled with a detectable marker;

(3) said third DNA probe labelled with a detectable marker is hybridized to said first single-stranded target DNA molecule; and

(4) said fourth DNA probe is hybridized to said first single-stranded target DNA molecule labelled with a detectable marker;

(D) exposing the resulting hybrid molecules of step (C) to said endonuclease, wherein said endonuclease recognizes a mismatch base pair selected from the group consisting of A/G, A/C, T/G and T/C, and

(1) binds to said mismatched base pair in said hybrid molecules to form an enzyme-DNA complex which is labelled, or

(2) cleaves a errand containing said mismatched base to produce a cleaved DNA fragment which is labelled; and

(E) assaying for the presence of said enzyme-DNA complex which is labelled or said cleaved DNA fragment which is labelled,

(1) wherein when said endonuclease recognizes A/G or A/C, and forms a labelled enzyme-DNA complex or produces labelled cleaved DNA fragments when exposed to the hybrid molecule obtained in step (C) (4), said nucleotide base pair at said point mutation site is A/T,

(2) wherein when said endonuclease recognizes T/G or T/C, and forms a labelled enzyme-DNA complex or produces labelled cleaved DNA fragments when exposed to the hybrid molecule obtained in step (C) (2), said nucleotide base pair at said point mutation site is A/T,

(3) wherein when said endonuclease recognizes A/G or A/C, and forms a labelled enzyme-DNA complex or produces labelled cleaved DNA fragments when exposed to the hybrid molecule obtained in step (C) (2), said nucleotide base pair at said point mutation site is T/A,

(4) wherein when said endonuclease recognizes T/G or T/C, and forms a labelled enzyme-DNA complex or produces labelled cleaved DNA fragments when exposed to the hybrid molecule obtained in step (C) (4), said nucleotide base pair at said point mutation site is T/A,

(5) wherein when said endonuclease recognizes A/G or T/G, and forms a labelled enzyme-DNA complex or produces labelled cleaved DNA fragments when exposed to the hybrid molecule obtained in step (C) (3), said nucleotide base pair at said point mutation site is G/C,

(6) wherein when said endonuclease recognizes A/C or T/C, and forms a labelled enzyme-DNA complex or produces labelled cleaved DNA fragments

when exposed to the hybrid molecule obtained in step (C) (1), said nucleotide base pair at said point mutation site te G/C,

(7) wherein when said endonuclease recognizes A/G or T/G, and forms a labelled enzyme-DNA complex or produces labelled cleaved DNA fragments when exposed to the hybrid molecule obtained in step (C) (1), said nucleotide base pair at said point mutation site is C/G, and

(8) wherein when said endonuclease recognizes A/C or T/C, and forms a labelled enzyme-DNA complex or produces labelled cleaved DNA fragments when exposed to the hybrid molecule obtained in step (C) (3), said nucleotide base pair at said point mutation site is C/G.

Dwg.0/0

```
=> d his

     (FILE 'HOME' ENTERED AT 12:37:50 ON 14 MAR 2004)
               SET COST OFF

     FILE 'HCAPLUS' ENTERED AT 12:38:07 ON 14 MAR 2004
L1             1 S WO98-GB2115/AP,PRN OR GB97-14971/AP,PRN
                 E LANE D/AU
                 E JACKSON S/AU
L2           131 S E3,E21
                 E JACKSON STEPHEN/AU
L3            13 S E3
L4           138 S E16,E17
L5             4 S E22
L6             3 S E23,E34
                 E LAKIN N/AU
L7            18 S E5,E7-E9,E11
                 E SMITH G/AU
L8           834 S E3,E12
L9             3 S E13
                 E SMITH GRAEME/AU
L10           64 S E3,E6-E8
L11          374 S E27,E30
                 E KUDOS/AP,CS
L12           15 S E4-E16
L13       527157 S ATM
L14         1767 S ATAX? TELANGIE?
L15         5842 S ATR
L16           83 S L2-L12 AND L13,L14
L17           10 S L2-L12 AND L15
L18           84 S L16,L17
L19           12 S L18 AND P53
                 E P53/CT
                 E E4+ALL
L20        15752 S E7-E10,E6+NT
L21           12 S L18 AND L20
L22           12 S L19,L21

     FILE 'REGISTRY' ENTERED AT 12:45:20 ON 14 MAR 2004
L23            1 S 182970-52-1

     FILE 'HCAPLUS' ENTERED AT 12:46:19 ON 14 MAR 2004
L24          122 S L23
L25          104 S (ATR OR CHECKPOINT)()PROTEIN KINASE
L26            2 S DNA DEPENDENT P53 KINASE ATR
L27           55 S PROTEIN KINASE ATR
L28            0 S ATR (1W) RAD3 RELATED PROTEIN KINASE
L29          251 S CHECKPOINT KINASE

     FILE 'REGISTRY' ENTERED AT 12:47:14 ON 14 MAR 2004
```

```
L30           1 S 182970-53-2

     FILE 'HCAPLUS' ENTERED AT 12:48:39 ON 14 MAR 2004
L31         387 S L30
L32         418 S ATM KINASE OR ATM PROTEIN KINASE OR PROTEIN KINASE ATM OR GEN
L33          20 S ATAX? TELANG? MUTAT? PROTEIN KINASE
L34          14 S L2-L12 AND L24-L29,L31-L33
L35          19 S L22,L34
L36          13 S L35 AND P53
L37           8 S L36 AND PHOSPHOR?
L38           5 S L36 NOT L37
                SEL DN AN 3
L39           4 S L38 NOT E1-E3
L40          12 S L37,L39
L41           6 S L35 NOT L36-L40
                SEL DN AN 2 5
L42           2 S L41 AND E4-E9
L43          14 S L40,L42 AND L1-L22,L24-L29,L31-L42
L44      533864 S L13-L15,L24-L29,L31-L33
L45         543 S L44 AND P53
L46         366 S L44 AND L20
L47         543 S L45,L46
L48         246 S L47 AND ?PHOSPHOR?
L49          19 S L48 AND SCREEN?
L50          70 S L47 AND (PD<=19970716 OR PRD<=19970716 OR AD<=19970716)
L51          12 S L50 AND L48
L52           2 S L50 AND SCREEN?
L53           7 S L50 AND ?ASSAY?
L54           2 S L50 AND (BIOCHEM?(L)METHOD?)/SC,SX
L55          18 S L51-L54
L56          17 S L55 NOT YTT?/TI
L57           2 S L43 AND (PD<=1997 OR PRD<=1997 OR AD<=1997)
L58          17 S L56,L57
L59          52 S L50 NOT L55-L58
                SEL DN AN 7 16 19 -22
                SEL DN AN 7 16 19-22
L60           6 S E76-E93
L61          23 S L58,L60 AND L1-L22,L24-L29,L31-L60
L62          17 S L61 AND ?RADIA?
L63          11 S L61 AND RADIA?/SC,SX
L64          18 S L62,L63
                SEL DN AN 3 13
L65           2 S E94-E99 AND L64
L66           5 S L61 NOT L64
L67           7 S L65,L66
L68          16 S L61-L66 NOT L67
                SEL HIT RN L61

     FILE 'REGISTRY' ENTERED AT 13:04:42 ON 14 MAR 2004
L69           1 S E100
L70           2 S L23,L30,L69

     FILE 'REGISTRY' ENTERED AT 13:05:14 ON 14 MAR 2004

     FILE 'HCAPLUS' ENTERED AT 13:05:20 ON 14 MAR 2004

     FILE 'BIOSIS' ENTERED AT 13:05:37 ON 14 MAR 2004
L71        3157 S ATAX? TELANG?
L72        2013 S L71 AND PY<=1997
L73          77 S L72 AND P53

     FILE 'WPIX' ENTERED AT 13:07:18 ON 14 MAR 2004
L74         180 S L14/BIX
```

```
L75          24 S L25/BIX OR L26/BIX OR L27/BIX OR L28/BIX OR L29/BIX
L76           5 S L32/BIX OR L33/BIX
L77         200 S L74-L76
L78          14 S L77 AND P53/BIX
L79           3 S L78 AND (JACKSON ? OR LAKIN ? OR SMITH ?)/AU
L80          11 S L78 NOT L79
L81           6 S L80 AND SCREEN?/BIX
L82           8 S L80 AND IDENT?/BIX
L83           2 S L80 NOT L81,L82
L84          12 S L79,L81,L82

     FILE 'WPIX' ENTERED AT 13:12:52 ON 14 MAR 2004

=>
```

```
Connecting via Winsock to STN


Welcome to STN International!  Enter x:x

LOGINID:ssspta1653hxp

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  JAN 27   Source of Registration (SR) information in REGISTRY updated
                   and searchable
 NEWS  4  JAN 27   A new search aid, the Company Name Thesaurus, available in
                   CA/CAplus
 NEWS  5  FEB 05   German (DE) application and patent publication number format
                   changes
 NEWS  6  MAR 03   MEDLINE and LMEDLINE reloaded
 NEWS  7  MAR 03   MEDLINE file segment of TOXCENTER reloaded
 NEWS  8  MAR 03   FRANCEPAT now available on STN
 NEWS  9  MAR 29   Pharmaceutical Substances (PS) now available on STN
 NEWS 10  MAR 29   WPIFV now available on STN
 NEWS 11  MAR 29   No connect hour charges in WPIFV until May 1, 2004
 NEWS 12  MAR 29   New monthly current-awareness alert (SDI) frequency in RAPRA

 NEWS EXPRESS  MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 13 APRIL 2004
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN Customer
  agreement.  Please note that this agreement limits use to scientific
  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 16:51:28 ON 22 APR 2004

=> file medline, biosis, dgene, fsta, wpids
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'MEDLINE' ENTERED AT 16:51:57 ON 22 APR 2004

FILE 'BIOSIS' ENTERED AT 16:51:57 ON 22 APR 2004
COPYRIGHT (C) 2004 BIOLOGICAL ABSTRACTS INC.(R)
```

FILE 'DGENE' ENTERED AT 16:51:57 ON 22 APR 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE 'FSTA' ENTERED AT 16:51:57 ON 22 APR 2004
COPYRIGHT (C) 2004 International Food Information Service

FILE 'WPIDS' ENTERED AT 16:51:57 ON 22 APR 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

=> s p53 () interact? () ATM
L1 0 P53 (W) INTERACT? (W) ATM

=> s (p53) interact? (ATM)
MISSING OPERATOR P53) INTERACT?
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s ATM and p53
L2 948 ATM AND P53

=> s l2 and interact?
L3 126 L2 AND INTERACT?

=> s l2 and binding
L4 185 L2 AND BINDING

=> s l4 and l3
L5 61 L4 AND L3

=> s l5 and binding assay
L6 2 L5 AND BINDING ASSAY

=> d l6 ti abs ibib tot

L6 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
TI Fanconi anemia type C and **p53** cooperate in apoptosis and tumorigenesis.
AB Fanconi anemia (FA) is a recessive genomic instability syndrome characterized by developmental defects, progressive bone marrow failure, and cancer. FA is genetically heterogeneous, however; the proteins encoded by different FA loci **interact** functionally with each other and with the BRCA1, BRCA2, and **ATM** gene products. Although patients with FA are highly predisposed to the development of myeloid leukemia and solid tumors, the alterations in biochemical pathways responsible for the progression of tumorigenesis in these patients remain unknown. FA cells are hypersensitive to a range of genotoxic and cellular stresses that activate signaling pathways mediating apoptosis. Here we show that ionizing radiation (IR) induces modestly elevated levels of **p53** in cells from FA type C (Fancc) mutant mice and that inactivation of Trp53 rescues tumor necrosis factor alpha-induced apoptosis in myeloid cells from Fancc-/- mice. Further, whereas Fancc-/- mice failed to form hematopoietic or solid malignancies, mice mutant at both Fancc and Trp53 developed tumors more rapidly than mice mutant at Trp53 alone. This shortened latency was associated with the appearance of tumor types that are found in patients with FA but not in mice mutant at Trp53 only. Collectively, these data demonstrate that **p53** and Fancc **interact** functionally to regulate apoptosis and tumorigenesis in Fancc-deficient cells.
ACCESSION NUMBER: 2004:30563 BIOSIS
DOCUMENT NUMBER: PREV200400023149
TITLE: Fanconi anemia type C and **p53** cooperate in apoptosis and tumorigenesis.
AUTHOR(S): Freie, Brian; Li, Xiaxin; Ciccone, Samantha L. M.; Nawa, Kathy; Cooper, Scott; Vogelweid, Catherine; Schantz,

Laurel; Haneline, Laura S.; Orazi, Attilio; Broxmeyer, Hal E.; Lee, Suk-Hee; Clapp, D. Wade [Reprint Author]

CORPORATE SOURCE: Cancer Research Institute, 1044 W Walnut St, R4/408, Indianapolis, IN, 46202, USA
dclapp@iupui.edu

SOURCE: Blood, (December 1 2003) Vol. 102, No. 12, pp. 4146-4152. print.
CODEN: BLOOAW. ISSN: 0006-4971.

DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Dec 2003
Last Updated on STN: 31 Dec 2003

L6 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

TI Recruitment of **ATM** protein to double strand DNA irradiated with ionizing radiation.

AB The product of the **ATM** gene, which is mutated in ataxia telangiectasia, is a nuclear phosphoprotein, and it involves the activation of the **p53** pathway after ionizing radiation. Here we show that the **ATM** protein is constitutively associated with double strand DNA and that the **interaction** increases when the DNA is exposed to ionizing radiation. The **ATM** protein also had affinity to restriction endonuclease PvuII-digested DNA, but not to UV-irradiated DNA nor X-irradiated single-stranded DNA. The immunoprecipitation experiment detected very weak association between **ATM** and DNA-PK proteins, and immunodepletion of DNA-PK showed little or no effect on the **interaction** of the **ATM** protein with damaged DNA, indicating that an **interaction** with DNA-PK might not be required for the recruitment of the **ATM** protein to damaged DNA. Furthermore, the association was also confirmed in xrs-5 and xrs-6e cells, which are Chinese hamster ovary mutant cell lines defective in Ku80 function. These results indicate that the **ATM** protein is recruited to the site of DNA damage and it recognizes double strand breaks by itself or through an association with other DNA-**binding** protein other than DNA-PK and Ku80 proteins.

ACCESSION NUMBER: 1999:518963 BIOSIS
DOCUMENT NUMBER: PREV199900518963
TITLE: Recruitment of **ATM** protein to double strand DNA irradiated with ionizing radiation.
AUTHOR(S): Suzuki, Keiji [Reprint author]; Kodama, Seiji; Watanabe, Masami
CORPORATE SOURCE: Laboratory of Radiation and Life Science, School of Pharmaceutical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki, 852, Japan
SOURCE: Journal of Biological Chemistry, (Sept. 3, 1999) Vol. 274, No. 36, pp. 25571-25575. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Dec 1999
Last Updated on STN: 3 Dec 1999

=> d his

(FILE 'HOME' ENTERED AT 16:51:28 ON 22 APR 2004)

FILE 'MEDLINE, BIOSIS, DGENE, FSTA, WPIDS' ENTERED AT 16:51:57 ON 22 APR 2004

L1 0 S P53 () INTERACT? () ATM
L2 948 S ATM AND P53
L3 126 S L2 AND INTERACT?
L4 185 S L2 AND BINDING
L5 61 S L4 AND L3

L6 2 S L5 AND BINDING ASSAY

=> s l5 and mdm-2
L7 0 L5 AND MDM-2

=> s l5 and phosphorylation
L8 44 L5 AND PHOSPHORYLATION

=> d l8 ti abs ibib tot

L8 ANSWER 1 OF 44 MEDLINE on STN
TI 53BP1 and NFBD1/MDC1-Nbs1 function in parallel **interacting** pathways activating ataxia-telangiectasia mutated (**ATM**) in response to DNA damage.
AB 53BP1 and NFBD1/MDC1 are recruited rapidly to sites of DNA double-strand breaks (DSBs), where they are hypothesized to function downstream of the ataxia-telangiectasia mutated (**ATM**) checkpoint kinase as "mediators" of DNA DSB signaling. To test this hypothesis, we suppressed 53BP1 and NFBD1/MDC1 expression by small interference RNA and monitored **ATM** autophosphorylation at Ser(1981) as a marker for **ATM** activation. Suppression of NFBD1/MDC1 led to decreased **ATM** activation and **phosphorylation** of **ATM** substrates. This phenotype was identical to that observed in cells with defective Nbs1 function and is consistent with recent observations identifying NFBD1/MDC1 as a component of the Mre11-Rad50-Nbs1 protein complex. In cells with wild-type Nbs1, suppression of 53BP1 expression had no effect on **ATM** activation but was associated with increased recruitment of NFBD1/MDC1 and Nbs1 to sites of DNA breaks, suggesting that decreased 53BP1 function might be compensated for by increased NFBD1/MDC1 and Nbs1 activity. Indeed, in cells with mutant Nbs1, suppression of 53BP1 led to decreased **ATM** activation and **phosphorylation** of **ATM** substrates. We conclude that DNA DSBs activate **ATM** through at least two independent pathways involving 53BP1 and NFBD1/MDC1-Nbs1, respectively.
ACCESSION NUMBER: 2003612313 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14695167
TITLE: 53BP1 and NFBD1/MDC1-Nbs1 function in parallel **interacting** pathways activating ataxia-telangiectasia mutated (**ATM**) in response to DNA damage.
AUTHOR: Mochan Tamara A; Venere Monica; DiTullio Richard A Jr; Halazonetis Thanos D
CORPORATE SOURCE: The Wistar Institute, Philadelphia, Pennsylvania 19104-4268, USA.
CONTRACT NUMBER: CA09171 (NCI)
CA09677 (NCI)
SOURCE: Cancer research, (2003 Dec 15) 63 (24) 8586-91.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200403
ENTRY DATE: Entered STN: 20031230
Last Updated on STN: 20040312
Entered Medline: 20040311

L8 ANSWER 2 OF 44 MEDLINE on STN
TI Regulatory **interactions** between the checkpoint kinase Chk1 and the proteins of the DNA-dependent protein kinase complex.
AB Checkpoints are biochemical pathways that provide cells a mechanism to detect DNA damage and respond by arresting the cell cycle to allow DNA repair. The conserved checkpoint kinase, Chk1, regulates mitotic progression in response to DNA damage by blocking the activation of

Cdk1/cyclin B. In this study, we investigate the regulatory **interaction** between Chk1 and members of the **Atm** family of kinases and the functional role of the C-terminal non-catalytic domains of Chk1. Chk1 stimulates the kinase activity of DNA-PK (protein kinase) complexes, which leads to increased **phosphorylation** of **p53** on Ser-15 and Ser-37. In addition, Chk1 stimulates DNA-PK-dependent end-joining reactions in vitro. We also show that Chk1 protein complexes bind to single-stranded DNA and DNA ends. These results indicate a connection between components that regulate the checkpoint pathways and DNA-PK complex proteins, which have a role in the repair of double strand breaks.

ACCESSION NUMBER: 2003363442 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12756247
TITLE: Regulatory **interactions** between the checkpoint kinase Chk1 and the proteins of the DNA-dependent protein kinase complex.
AUTHOR: Goudelock Dawn Marie; Jiang Kecheng; Pereira Elizabeth; Russell Beatriz; Sanchez Yolanda
CORPORATE SOURCE: Department of Molecular Genetics, Biochemistry, and Microbiology, University of Cincinnati College of Medicine, Cincinnati, Ohio 45267-0524, USA.
CONTRACT NUMBER: R01 CA84463 (NCI)
SOURCE: Journal of biological chemistry, (2003 Aug 8) 278 (32) 29940-7.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200309
ENTRY DATE: Entered STN: 20030805
Last Updated on STN: 20030925
Entered Medline: 20030924

L8 ANSWER 3 OF 44 MEDLINE on STN
TI Accumulation of checkpoint protein 53BP1 at DNA breaks involves its **binding** to phosphorylated histone H2AX.
AB 53BP1 participates in the cellular response to DNA damage. Like many proteins involved in the DNA damage response, 53BP1 becomes hyperphosphorylated after radiation and colocalizes with phosphorylated H2AX in megabase regions surrounding the sites of DNA strand breaks. However, it is not yet clear whether the **phosphorylation** status of 53BP1 determines its localization or vice versa. In this study we mapped a region upstream of the 53BP1 C terminus that is required and sufficient for the recruitment of 53BP1 to these DNA break areas. In vitro assays revealed that this region binds to phosphorylated but not unphosphorylated H2AX. Moreover, using H2AX-deficient cells reconstituted with wild-type or a **phosphorylation**-deficient mutant of H2AX, we have shown that **phosphorylation** of H2AX at serine 140 is critical for efficient 53BP1 foci formation, implying that a direct **interaction** between 53BP1 and phosphorylated H2AX is required for the accumulation of 53BP1 at DNA break sites. On the other hand, radiation-induced **phosphorylation** of the 53BP1 N terminus by the **ATM** (ataxia-telangiectasia mutated) kinase is not essential for 53BP1 foci formation and takes place independently of 53BP1 redistribution. Thus, these two damage-induced events, hyperphosphorylation and relocalization of 53BP1, occur independently in the cell.

ACCESSION NUMBER: 2003243845 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12697768
TITLE: Accumulation of checkpoint protein 53BP1 at DNA breaks involves its **binding** to phosphorylated histone H2AX.
AUTHOR: Ward Irene M; Minn Kay; Jorda Katherine G; Chen Junjie

CORPORATE SOURCE: Department of Oncology, Mayo Clinic and Foundation, Rochester, Minnesota 55905, USA.
SOURCE: Journal of biological chemistry, (2003 May 30) 278 (22) 19579-82.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030528
Last Updated on STN: 20030711
Entered Medline: 20030710

L8 ANSWER 4 OF 44 MEDLINE on STN
TI MDC1 is coupled to activated CHK2 in mammalian DNA damage response pathways.
AB Forkhead-homology-associated (FHA) domains function as protein-protein modules that recognize phosphorylated serine/threonine motifs. **Interactions** between FHA domains and phosphorylated proteins are thought to have essential roles in the transduction of DNA damage signals; however, it is unclear how FHA-domain-containing proteins participate in mammalian DNA damage responses. Here we report that a FHA-domain-containing protein-mediator of DNA damage checkpoint protein 1 (MDC1; previously known as KIAA0170)--is involved in DNA damage responses. MDC1 localizes to sites of DNA breaks and associates with CHK2 after DNA damage. This association is mediated by the MDC1 FHA domain and the phosphorylated Thr 68 of CHK2. Furthermore, MDC1 is phosphorylated in an **ATM**/CHK2-dependent manner after DNA damage, suggesting that MDC1 may function in the **ATM**-CHK2 pathway. Consistent with this hypothesis, suppression of MDC1 expression results in defective S-phase checkpoint and reduced apoptosis in response to DNA damage, which can be restored by the expression of wild-type MDC1 but not MDC1 with a deleted FHA domain. Suppression of MDC1 expression results in decreased **p53** stabilization in response to DNA damage. These results suggest that MDC1 is recruited through its FHA domain to the activated CHK2, and has a critical role in CHK2-mediated DNA damage responses.
ACCESSION NUMBER: 2003095328 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12607004
TITLE: MDC1 is coupled to activated CHK2 in mammalian DNA damage response pathways.
AUTHOR: Lou Zhenkun; Minter-Dykhouse Katherine; Wu Xianglin; Chen Junjie
CORPORATE SOURCE: Department of Oncology, Mayo Foundation, Rochester, Minnesota 55905, USA.
SOURCE: Nature, (2003 Feb 27) 421 (6926) 957-61.
Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20030228
Last Updated on STN: 20030331
Entered Medline: 20030328

L8 ANSWER 5 OF 44 MEDLINE on STN
TI **Phosphorylation** and hsp90 **binding** mediate heat shock stabilization of **p53**.
AB The **p53** tumor suppressor is stabilized and activated by diverse stress signals. In this study, we investigated the mechanism of **p53** activation by heat shock. We found that heat shock inhibited **p53** ubiquitination and caused accumulation of **p53** at the post-transcriptional level. Heat shock induced **phosphorylation**

of **p53** at serine 15 in an **ATM** kinase-dependent fashion, which may contribute partially to heat-induced **p53** accumulation. However, **p53** accumulation also occurred after heat shock in **ATM**-deficient cells. Heat shock induced conformational change of wild type **p53** and **binding** to hsp90. Inhibition of hsp90-**p53 interaction** by geldanamycin prevented **p53** accumulation partially in **ATM** -wild type cells and completely in **ATM**-deficient cells. Therefore, **phosphorylation** and **interaction** with hsp90 both contribute to stabilization of **p53** after heat shock.

ACCESSION NUMBER: 2003017905 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12427754
TITLE: **Phosphorylation** and hsp90 **binding** mediate heat shock stabilization of **p53**.
AUTHOR: Wang Chuangui; Chen Jiandong
CORPORATE SOURCE: Molecular Oncology Program, H. Lee Moffitt Comprehensive Cancer Center and Research Institute, Tampa, Florida 33612, USA.
CONTRACT NUMBER: CA88406 (NCI)
SOURCE: Journal of biological chemistry, (2003 Jan 17) 278 (3) 2066-71.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20030114
Last Updated on STN: 20030215
Entered Medline: 20030214

L8 ANSWER 6 OF 44 MEDLINE on STN
TI Kinetochore localisation of the DNA damage response component 53BP1 during mitosis.
AB 53BP1 is a vertebrate BRCT motif protein, originally described as a direct **interactor** of **p53**, which has recently been shown to be implicated in the early response to DNA damage. Upon DNA damage, 53BP1 re-localises to discrete nuclear foci that are thought to represent sites of DNA lesions and becomes hyperphosphorylated. Several observations suggest that 53BP1 is a direct substrate for the ataxia telangiectasia mutated (**ATM**) kinase. So far, 53BP1 behaviour during mitosis has not been reported in detail. We have examined 53BP1 subcellular distribution in mitotic cells using several antibodies against 53BP1, and ectopic expression of GFP-tagged 53BP1. We found that 53BP1 significantly colocalised with CENP-E to kinetochores. 53BP1 is loaded to kinetochores in prophase, before CENP-E, and is released by mid-anaphase. By expressing various GFP-tagged 53BP1 truncations, the kinetochore **binding** domain has been mapped to a 380 residue portion of the protein that excludes the nuclear localisation signal and the BRCT motifs. Like many kinetochore-associated proteins involved in mitotic checkpoint signalling, more 53BP1 appears to accumulate on the kinetochores of chromosomes not aligned on the metaphase plate. Finally, we show that 53BP1 is hyperphosphorylated in mitotic cells, and undergoes an even higher level of **phosphorylation** in response to spindle disruption with colcemid. Our data suggest that 53BP1 may have a role in checkpoint signalling during mitosis and provide the evidence that DNA damage response machinery and mitotic checkpoint may share common molecular components.

ACCESSION NUMBER: 2002075893 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11801725
TITLE: Kinetochore localisation of the DNA damage response component 53BP1 during mitosis.
AUTHOR: Jullien Denis; Vagnarelli Paola; Earnshaw William C; Adachi Yasuhisa

CORPORATE SOURCE: The Wellcome Trust Centre for Cell Biology, Institute of Cell and Molecular Biology, The University of Edinburgh, King's Buildings, Edinburgh EH9 3JR, UK.
SOURCE: Journal of cell science, (2002 Jan 1) 115 (Pt 1) 71-9. Journal code: 0052457. ISSN: 0021-9533.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020501
Entered Medline: 20020430

L8 ANSWER 7 OF 44 MEDLINE on STN

TI Plk3 functionally links DNA damage to cell cycle arrest and apoptosis at least in part via the **p53** pathway.

AB Polo-like kinase 3 (Plk3, previously termed Prk) contributes to regulation of M phase of the cell cycle (Ouyang, B., Pan, H., Lu, L., Li, J., Stambrook, P., Li, B., and Dai, W. (1997) J. Biol. Chemical 272, 28646-28651). Plk3 physically **interacts** with Cdc25C and phosphorylates this protein phosphatase predominantly on serine 216 (Ouyang, B., Li, W., Pan, H., Meadows, J., Hoffmann, I., and Dai, W. (1999) Oncogene 18, 6029-6036), suggesting that the role of Plk3 in mitosis is mediated, at least in part, through direct regulation of Cdc25C. Here we show that ectopic expression of a kinase-active Plk3 (Plk3-A) induced apoptosis. In response to DNA damage, the kinase activity of Plk3 was rapidly increased in an **ATM**-dependent manner, whereas that of Plk1 was markedly inhibited. Recombinant Plk3 phosphorylated in vitro a glutathione S-transferase fusion protein containing **p53**, but not glutathione S-transferase alone. Recombinant Plk1 also phosphorylated **p53** but on residues that differed from those targeted by Plk3. Co-immunoprecipitation and pull-down assays demonstrated that Plk3 physically **interacted** with **p53** and that this **interaction** was enhanced upon DNA damage. In vitro kinase assays followed by immunoblotting showed that serine 20 of **p53** was a target of Plk3. Furthermore, expression of a kinase-defective Plk3 mutant (Plk3(K52R)) resulted in significant reduction of **p53 phosphorylation** on serine 20, which was correlated with a decrease in the expression of p21 and with a concomitant increase in cell proliferation. These results strongly suggest that Plk3 functionally links DNA damage to cell cycle arrest and apoptosis via the **p53** pathway.

ACCESSION NUMBER: 2001652581 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11551930
TITLE: Plk3 functionally links DNA damage to cell cycle arrest and apoptosis at least in part via the **p53** pathway.
AUTHOR: Xie S; Wu H; Wang Q; Cogswell J P; Husain I; Conn C; Stambrook P; Jhanwar-Uniyal M; Dai W
CORPORATE SOURCE: American Health Foundation, Valhalla, New York 10595, USA.
CONTRACT NUMBER: RO1-74229
SOURCE: Journal of biological chemistry, (2001 Nov 16) 276 (46) 43305-12. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011114
Last Updated on STN: 20030105
Entered Medline: 20011226

L8 ANSWER 8 OF 44 MEDLINE on STN

TI Critical roles for the serine 20, but not the serine 15, **phosphorylation** site and for the polyproline domain in regulating **p53** turnover.

AB The **p53** tumour suppressor protein is a short-lived transcription factor that becomes stabilized in response to a wide range of cellular stresses. Ubiquitination and the targeting of **p53** for degradation by the proteasome are mediated by Mdm2 (mouse double minute clone 2), a negative regulatory partner of **p53**. Previous studies have suggested that DNA-damage-induced **phosphorylation** of **p53** at key N-terminal sites has a pivotal role in regulating the **interaction** with Mdm2 but the precise role of **phosphorylation** of serines 15 and 20 is still unclear. Here we show that replacement of serine 15 and a range of other key N-terminal **phosphorylation** sites with alanine, which cannot be phosphorylated, has little effect on the ubiquitination and degradation of full-length human **p53**. In contrast, replacement of serine 20 makes **p53** highly sensitive to Mdm2-mediated turnover. These results define distinct roles for serines 15 and 20, two sites previously demonstrated to be dependent on **phosphorylation** through mechanisms mediated by DNA damage and **ATM** (ataxia telangiectasia mutated). We also show that the polyproline region of **p53**, a domain that has a key role in **p53**-induced apoptosis, exerts a critical influence over the Mdm2-mediated turnover of **p53**.

ACCESSION NUMBER: 2001536345 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11583595
TITLE: Critical roles for the serine 20, but not the serine 15, **phosphorylation** site and for the polyproline domain in regulating **p53** turnover.
AUTHOR: Dumaz N; Milne D M; Jardine L J; Meek D W
CORPORATE SOURCE: Biomedical Research Centre, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, UK.
SOURCE: Biochemical journal, (2001 Oct 15) 359 (Pt 2) 459-64. Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011004
Last Updated on STN: 20020420
Entered Medline: 20011204

L8 ANSWER 9 OF 44 MEDLINE on STN

TI Negative cell cycle regulation and DNA damage-inducible **phosphorylation** of the BRCT protein 53BP1.

AB In a screen designed to discover suppressors of mitotic catastrophe, we identified the Xenopus ortholog of 53BP1 (X53BP1), a BRCT protein previously identified in humans through its ability to bind the **p53** tumor suppressor. X53BP1 transcripts are highly expressed in ovaries, and the protein **interacts** with Xp53 throughout the cell cycle in embryonic extracts. However, no **interaction** between X53BP1 and Xp53 can be detected in somatic cells, suggesting that the association between the two proteins may be developmentally regulated. X53BP1 is modified via **phosphorylation** in a DNA damage-dependent manner that correlates with the dispersal of X53BP1 into multiple foci throughout the nucleus in somatic cells. Thus, X53BP1 can be classified as a novel participant in the DNA damage response pathway. We demonstrate that X53BP1 and its human ortholog can serve as good substrates in vitro as well as in vivo for the **ATM** kinase. Collectively, our results reveal that 53BP1 plays an important role in the checkpoint response to DNA damage, possibly in collaboration with **ATM**.

ACCESSION NUMBER: 2001286613 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11042216
TITLE: Negative cell cycle regulation and DNA damage-inducible

phosphorylation of the BRCT protein 53BP1.
AUTHOR: Xia Z; Morales J C; Dunphy W G; Carpenter P B
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Texas Health Sciences Center, Houston 77030, USA.
SOURCE: Journal of biological chemistry, (2001 Jan 26) 276 (4) 2708-18.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF281071
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010625
Last Updated on STN: 20030105
Entered Medline: 20010621

L8 ANSWER 10 OF 44 MEDLINE on STN
TI **Phosphorylation** and rapid relocalization of 53BP1 to nuclear foci upon DNA damage.
AB 53BP1 is a human BRCT protein that was originally identified as a **p53-interacting** protein by the Saccharomyces cerevisiae two-hybrid screen. Although the carboxyl-terminal BRCT domain shows similarity to Crb2, a DNA damage checkpoint protein in fission yeast, there is no evidence so far that implicates 53BP1 in the checkpoint. We have identified a Xenopus homologue of 53BP1 (XL53BP1). XL53BP1 is associated with chromatin and, in some cells, localized to a few large foci under normal conditions. Gamma-ray irradiation induces increased numbers of the nuclear foci in a dose-dependent manner. The damage-induced 53BP1 foci appear rapidly (in 30 min) after irradiation, and de novo protein synthesis is not required for this response. In human cells, 53BP1 foci colocalize with Mrel1 foci at later stages of the postirradiation period. XL53BP1 is hyperphosphorylated after X-ray irradiation, and inhibitors of **ATM**-related kinases delay the relocalization and reduce the **phosphorylation** of XL53BP1 in response to X-irradiation. In AT cells, which lack **ATM** kinase, the irradiation-induced responses of 53BP1 are similarly affected. These results suggest a role for 53BP1 in the DNA damage response and/or checkpoint control which may involve signaling of damage to **p53**.
ACCESSION NUMBER: 2001204624 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11238909
TITLE: **Phosphorylation** and rapid relocalization of 53BP1 to nuclear foci upon DNA damage.
AUTHOR: Anderson L; Henderson C; Adachi Y
CORPORATE SOURCE: The Wellcome Trust Centre for Cell Biology, Institute of Cell & Molecular Biology, University of Edinburgh, Edinburgh EH9 3JR, United Kingdom.
SOURCE: Molecular and cellular biology, (2001 Mar) 21 (5) 1719-29.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010417
Last Updated on STN: 20030218
Entered Medline: 20010412

L8 ANSWER 11 OF 44 MEDLINE on STN
TI Genetic evidence of a role for **ATM** in functional **interaction** between human T-cell leukemia virus type 1 Tax and **p53**.
AB Recent evidence from several investigators suggest that the human T-cell

leukemia virus type 1 Tax oncoprotein represses the transcriptional activity of the tumor suppressor protein, **p53**. An examination of published findings reveals serious controversy as to the mechanism(s) utilized by Tax to inhibit **p53** activity and whether the same mechanism is used by Tax in adherent and suspension cells. Here, we have investigated Tax-**p53** **interaction** simultaneously in adherent epithelial (HeLa and Saos) and suspension T-lymphocyte (Jurkat) cells. Our results indicate that Tax activity through the CREB/CREB-**binding** protein (CBP), but not NF-kappaB, pathway is needed to repress the transcriptional activity of **p53** in all tested cell lines. However, we did find that while CBP **binding** by Tax is necessary, it is not sufficient for inhibiting **p53** function. Based on knockout cell studies, we correlated a strong genetic requirement for the **ATM**, but not protein kinase-dependent DNA, protein in conferring a Tax-**p53**-repressive phenotype.

ACCESSION NUMBER: 2001074790 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11119608
TITLE: Genetic evidence of a role for **ATM** in functional **interaction** between human T-cell leukemia virus type 1 Tax and **p53**.
AUTHOR: Van P L; Yim K W; Jin D Y; Dapolito G; Kurimasa A; Jeang K T
CORPORATE SOURCE: Laboratory of Molecular Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA.
SOURCE: Journal of virology, (2001 Jan) 75 (1) 396-407. Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20021217
Entered Medline: 20010104

L8 ANSWER 12 OF 44 MEDLINE on STN
TI **Phosphorylation** of Ser-20 mediates stabilization of human **p53** in response to DNA damage.
AB Stabilization of **p53** in response to DNA damage is caused by its dissociation from Mdm2, a protein that targets **p53** for degradation in the proteasome. Dissociation of **p53** from Mdm2 could be caused by DNA damage-induced **p53** posttranslational modifications. The **ATM** and ATR kinases, whose activation in response to ionizing radiation (IR) and UV light, respectively, is required for **p53** stabilization, directly phosphorylate **p53** on Ser-15. However, **phosphorylation** of Ser-15 is critical for the apoptotic activity of **p53** and not for **p53** stabilization. Thus, whether any **p53** modifications, and which, underlie disruption of the **p53**-Mdm2 complex after DNA damage remains to be determined. We analyzed the IR- and UV light-induced stabilization of **p53** proteins with substitutions of Ser known to be posttranslationally modified after DNA damage. Substitution of Ser-20 was sufficient to abrogate **p53** stabilization in response to both IR and UV light. Furthermore, both IR and UV light induced **phosphorylation** of **p53** on Ser-20, which involved the majority of nuclear **p53** protein and weakened the **interaction** of **p53** with Mdm2 in vitro. **ATM** and ATR cannot phosphorylate **p53** on Ser-20. We therefore propose that **ATM** and ATR activate an, as yet unidentified, kinase that stabilizes **p53** by phosphorylating it on Ser-20.

ACCESSION NUMBER: 2000040627 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10570149
TITLE: **Phosphorylation** of Ser-20 mediates stabilization

of human **p53** in response to DNA damage.
AUTHOR: Chehab N H; Malikzay A; Stavridi E S; Halazonetis T D
CORPORATE SOURCE: Department of Molecular Genetics, The Wistar Institute, Philadelphia, PA 19104, USA.
CONTRACT NUMBER: CA76367 (NCI)
T32 CA09171 (NCI)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1999 Nov 23) 96 (24) 13777-82. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000114
Last Updated on STN: 20000114
Entered Medline: 20000106

L8 ANSWER 13 OF 44 MEDLINE on STN
TI DNA damage induced **p53** stabilization: no indication for an involvement of **p53 phosphorylation**.
AB Abundance and activity of **p53** are predominantly regulated posttranslationally. Structural disturbance in transcribed genes induced by radiation, e.g. DNA damage, or by transcriptional inhibitors cause **p53** protein stabilization by a yet unknown mechanism. Using stable and transient transfections for the analysis of **p53** mutant proteins, we have ruled out a role in stabilization by UV, gamma irradiation or actinomycin C for the following putative **phosphorylation** sites in the **p53** protein: serines 6, 9, 15, 33, 315 and 392, and threonine 18. By double mutation combinations of phosphorylations were also ruled out; 6,9; 15,18; 15,37. These mutations eliminate modifications by casein kinases I and II, DNA-PK, **ATM**, CDK and JNK. Also the 30 carboxyterminal amino acids are not required for induced **p53** stabilization. Thus neither phosphorylations of individual amino acids nor **interactions** of the carboxyterminus of **p53** with cellular macromolecules appear to play a role in the stabilization process. The only single prerequisite for induced stabilization of **p53** is its prior destabilization by Mdm2. However, the level of active Mdm2 must be controlled carefully: overexpression of Mdm2 inhibits UV induced **p53** stabilization.
ACCESSION NUMBER: 1999223132 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10208433
TITLE: DNA damage induced **p53** stabilization: no indication for an involvement of **p53 phosphorylation**.
AUTHOR: Blattner C; Tobiasch E; Litfen M; Rahmsdorf H J; Herrlich P
CORPORATE SOURCE: Forschungszentrum Karlsruhe, Institut fur Genetik, Universitat Karlsruhe, Germany.
SOURCE: Oncogene, (1999 Mar 4) 18 (9) 1723-32. Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990614
Last Updated on STN: 19990614
Entered Medline: 19990601

L8 ANSWER 14 OF 44 MEDLINE on STN
TI Replication-mediated DNA damage by camptothecin induces **phosphorylation** of RPA by DNA-dependent protein kinase and dissociates RPA:DNA-PK complexes.
AB Replication protein A (RPA) is a DNA single-strand **binding**

protein essential for DNA replication, recombination and repair. In human cells treated with the topoisomerase inhibitors camptothecin or etoposide (VP-16), we find that RPA2, the middle-sized subunit of RPA, becomes rapidly phosphorylated. This response appears to be due to DNA-dependent protein kinase (DNA-PK) and to be independent of **p53** or the ataxia telangiectasia mutated (**ATM**) protein. RPA2 **phosphorylation** in response to camptothecin required ongoing DNA replication. Camptothecin itself partially inhibited DNA synthesis, and this inhibition followed the same kinetics as DNA-PK activation and RPA2 **phosphorylation**. DNA-PK activation and RPA2 **phosphorylation** were prevented by the cell-cycle checkpoint abrogator 7-hydroxystaurosporine (UCN-01), which markedly potentiates camptothecin cytotoxicity. The DNA-PK catalytic subunit (DNA-PKcs) was found to bind RPA which was replaced by the Ku autoantigen upon camptothecin treatment. DNA-PKcs **interacted** directly with RPA1 in vitro. We propose that the encounter of a replication fork with a topoisomerase-DNA cleavage complex could lead to a juxtaposition of replication fork-associated RPA and DNA double-strand end-associated DNA-PK, leading to RPA2 **phosphorylation** which may signal the presence of DNA damage to an S-phase checkpoint mechanism. Keywords: camptothecin/DNA damage/DNA-dependent protein kinase/RPA2 **phosphorylation**

ACCESSION NUMBER: 1999164105 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10064605
TITLE: Replication-mediated DNA damage by camptothecin induces **phosphorylation** of RPA by DNA-dependent protein kinase and dissociates RPA:DNA-PK complexes.
AUTHOR: Shao R G; Cao C X; Zhang H; Kohn K W; Wold M S; Pommier Y
CORPORATE SOURCE: Laboratory of Molecular Pharmacology, Division of Basic Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892-4255, USA.
SOURCE: EMBO journal, (1999 Mar 1) 18 (5) 1397-406.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990511
Last Updated on STN: 20030218
Entered Medline: 19990429

L8 ANSWER 15 OF 44 MEDLINE on STN
TI Determination of cell fate by c-Abl activation in the response to DNA damage.
AB The cellular response to DNA damage includes growth arrest and activation of DNA repair. Certain insights into how DNA damage is converted into intracellular signals that control the genotoxic stress response have been derived from the finding that the c-Abl protein tyrosine kinase is activated by ionizing radiation and other DNA-damaging agents. c-Abl associates with the DNA-dependent protein kinase (DNA-PK) and is activated by DNA-PK-dependent **phosphorylation**. The ataxia telangiectasia mutated (**ATM**) gene product also contributes to c-Abl activation. The demonstration that c-Abl binds to **p53**, induces the transactivation function of **p53** and activates p21 expression has supported involvement of c-Abl in regulation of the **p53** -dependent G1 arrest response. **Interaction** between c-Abl and the Rad51 protein has also provided support for involvement of c-Abl in recombinational repair of DNA strand breaks. Defects in G1 arrest and repair predispose to replication of damaged templates and, in the event of irreparable DNA lesions, induction of apoptosis. The available evidence indicates that c-Abl effects a proapoptotic function by a mechanism largely independent of **p53**. c-Abl also functions as an upstream effector of the proapoptotic JNK/SAPK and p38 MAPK pathways. In addition,

c-Abl-dependent inhibition of PI 3-kinase contributes to the induction of apoptosis. The findings thus suggest that, in response to genotoxic stress, c-Abl functions in determining cell fate, that is growth arrest and repair or induction of apoptosis. The physiologic function of c-Abl may reside in control of the cellular response to DNA strand breaks that occur during DNA replication, genetic recombination and gene rearrangements.

ACCESSION NUMBER: 1999114031 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9916993
TITLE: Determination of cell fate by c-Abl activation in the response to DNA damage.
AUTHOR: Kharbanda S; Yuan Z M; Weichselbaum R; Kufe D
CORPORATE SOURCE: Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: CA 55241 (NCI)
CA29431 (NCI)
SOURCE: Oncogene, (1998 Dec 24) 17 (25) 3309-18. Ref: 177
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990301
Last Updated on STN: 19990301
Entered Medline: 19990216

L8 ANSWER 16 OF 44 MEDLINE on STN
TI **ATM** associates with and phosphorylates **p53**: mapping the region of **interaction**.
AB The human genetic disorder ataxia-telangiectasia (AT) is characterized by immunodeficiency, progressive cerebellar ataxia, radiosensitivity, cell cycle checkpoint defects and cancer predisposition. The gene mutated in this syndrome, **ATM** (for AT mutated), encodes a protein containing a phosphatidyl-inositol 3-kinase (PI-3 kinase)-like domain. **ATM** also contains a proline-rich region and a leucine zipper, both of which implicate this protein in signal transduction. The proline-rich region has been shown to bind to the SH3 domain of c-Abl, which facilitates its **phosphorylation** and activation by **ATM**. Previous results have demonstrated that AT cells are defective in the G1/S checkpoint activated after radiation damage and that this defect is attributable to a defective **p53** signal transduction pathway. We report here direct **interaction** between **ATM** and **p53** involving two regions in **ATM**, one at the amino terminus and the other at the carboxy terminus, corresponding to the PI-3 kinase domain. Recombinant **ATM** protein phosphorylates **p53** on serine 15 near the N terminus. Furthermore, ectopic expression of **ATM** in AT cells restores normal ionizing radiation (IR)-induced **phosphorylation** of **p53**, whereas expression of **ATM** antisense RNA in control cells abrogates the rapid IR-induced **phosphorylation** of **p53** on serine 15. These results demonstrate that **ATM** can bind **p53** directly and is responsible for its serine 15 **phosphorylation**, thereby contributing to the activation and stabilization of **p53** during the IR-induced DNA damage response.

ACCESSION NUMBER: 1999057351 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9843217
TITLE: **ATM** associates with and phosphorylates **p53**: mapping the region of **interaction**.
AUTHOR: Khanna K K; Keating K E; Kozlov S; Scott S; Gatei M; Hobson K; Taya Y; Gabrielli B; Chan D; Lees-Miller S P; Lavin M F
CORPORATE SOURCE: The Queensland Institute of Medical Research, PO Royal

Brisbane Hospital, Australia.. kumkumK@qimr.edu.au
SOURCE: Nature genetics, (1998 Dec) 20 (4) 398-400.
Journal code: 9216904. ISSN: 1061-4036.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981221

L8 ANSWER 17 OF 44 MEDLINE on STN
TI **ATM**-dependent activation of **p53** involves dephosphorylation and association with 14-3-3 proteins.
AB The **p53** tumour-suppressor protein is a sequence-specific DNA-**binding** transcription factor that induces cell cycle arrest or apoptosis in response to genotoxic stress. Activation of **p53** by DNA-damaging agents is critical for eliminating cells with damaged genomic DNA and underlies the apoptotic response of human cancers treated with ionizing radiation (IR) and radiomimetic drugs. The molecular mechanisms by which DNA damage activates **p53** have not been elucidated. Both the levels of **p53** protein and its affinity for specific DNA sequences increase in response to genotoxic stress. In vitro, the affinity of **p53** for DNA is regulated by its carboxy-terminus. We therefore examined whether this region of **p53** is targeted by DNA-damage signalling pathways in vivo. In nonirradiated cells, serines 376 and 378 of **p53** were phosphorylated. IR led to dephosphorylation of Ser376, creating a consensus **binding** site for 14-3-3 proteins and leading to association of **p53** with 14-3-3. In turn, this increased the affinity of **p53** for sequence-specific DNA. Consistent with the lack of **p53** activation by IR in ataxia telangiectasia (AT; refs 14,15), neither Ser376 dephosphorylation, nor the **interaction** of **p53** with 14-3-3 proteins occurred in AT cells.
ACCESSION NUMBER: 1998282098 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9620776
TITLE: **ATM**-dependent activation of **p53** involves dephosphorylation and association with 14-3-3 proteins.
AUTHOR: Waterman M J; Stavridi E S; Waterman J L; Halazonetis T D
CORPORATE SOURCE: Department of Molecular Genetics, The Wistar Institute, Philadelphia, Pennsylvania 19104-4268, USA.
SOURCE: Nature genetics, (1998 Jun) 19 (2) 175-8.
Journal code: 9216904. ISSN: 1061-4036.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980713
Last Updated on STN: 19980713
Entered Medline: 19980701

L8 ANSWER 18 OF 44 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
TI Molecular Mechanisms Mediating Anti-Myeloma Activity of Proteasome Inhibitor PS-341.
AB PS-341 (pyrazylcarbonyl-Phe-Leu-boronate) is a peptide boronate proteasome inhibitors which induces apoptosis in drug resistant multiple myeloma (MM) cells, inhibits **binding** of MM cells in the bone marrow microenvironment, and inhibits cytokines mediating MM cell growth, survival, drug resistance, and migration in vitro. Moreover, PS-341 also inhibits human MM cell growth and prolongs survival in a SCID mouse model. Most importantly, PS-341 has achieved responses, even complete responses,

in a Phase II clinical trial treating patients with relapsed MM refractory to conventional therapies, and has an acceptable toxicity profile. In this study, we further defined the molecular mechanisms whereby PS-341 mediates anti-MM activity. PS-341 treatment (20 nM, up to 16 h incubation) transiently upregulates **p53** protein expression in MM.1S cells, with peak expression at 8 h. PS-341 also induces transient **p53 phosphorylation** on serine 15 (Ser15), without **phosphorylation** of Ser 6, 9, 20, 37, 46, or 392 residues. MDM2 protein is similarly transiently upregulated after PS-341 treatment, with peak protein expression observed at 6 h. Importantly, PS-341 also induces **phosphorylation** (Ser15) and upregulation of **p53** and MDM2 protein expression in freshly isolated patient MM cells. These results suggest that PS-341 induces DNA damage in both MM cell lines and patient MM cells. We demonstrated that PS-341 induces co-immunoprecipitation of **p53** with c-Jun NH2-terminal kinase (JNK) in a time-dependent fashion; **phosphorylation** of JNK, as well as both upstream (SEK-1) and down stream (c-Jun and ATF-2) proteins; as well as significant (2.5 - 72 fold) increase in heat shock proteins transcription in a time-dependent fashion, assessed by gene microarray. These results indicate that PS-341 induces a stress response, as well as **interaction** of **p53** and JNK, in MM cell lines. The JNK specific inhibitor SP600125 blocks **phosphorylation** of JNK triggered by PS-341 in a dose-dependent fashion; and PS-341-induced cytotoxicity in MM.1S cells, without blocking PS-341-induced **p53 phosphorylation** or induction of MDM2. These results suggest that signaling between **p53** and JNK is through **p53** to JNK, but not via JNK to **p53**, and that JNK plays a critical role in mediating PS-341-induced apoptosis via activation of caspase-3. Most importantly, PS-341 cleaves DNA-PKcs and **ATM** in a time-, and dose-dependent fashion in MM cell lines, as well as patient's MM cells suggesting that PS-341 impairs DNA repair. Pan-caspase inhibitor Z-VAD-FMK and caspase-8 inhibitor Z-IETD-FMK completely abrogate DNA-PKcs and **ATM** cleavage induced by PS-341. These results suggest that PS-341 induces: DNA-PKcs and **ATM** cleavage; **phosphorylation** of **p53** and MDM2 cleavage via caspase-3 activation; and **ATM** or ATR activation by activation of caspase-3 via caspase-8. Given the early clinical promise of and favorable toxicity profile of PS-341 in patients with relapsed refractory MM, these studies provide the framework for further clinical evaluation of PS-341, alone and coupled with conventional or other novel therapies, to improve patient outcome in MM.

ACCESSION NUMBER: 2003:357350 BIOSIS
DOCUMENT NUMBER: PREV200300357350
TITLE: Molecular Mechanisms Mediating Anti-Myeloma Activity of Proteasome Inhibitor PS-341.
AUTHOR(S): Hideshima, Teru [Reprint Author]; Mitsiades, Constantine [Reprint Author]; Akiyama, Masaharu [Reprint Author]; Hayashi, Toshiaki [Reprint Author]; Chauhan, Dharminder [Reprint Author]; Richardson, Paul G. [Reprint Author]; Schlossman, Robert L. [Reprint Author]; Podar, Klaus [Reprint Author]; Munshi, Nikhil C. [Reprint Author]; Mitsiades, Nicholas [Reprint Author]; Anderson, Kenneth C. [Reprint Author]
CORPORATE SOURCE: Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Boston, MA, USA
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 3215. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English

ENTRY DATE: Entered STN: 6 Aug 2003
Last Updated on STN: 6 Aug 2003

L8 ANSWER 19 OF 44 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
TI **Phosphorylation** and hsp90 **binding** mediate heat shock stabilization of **p53**.
AB The **p53** tumor suppressor is stabilized and activated by diverse stress signals. In this study, we investigated the mechanism of **p53** activation by heat shock. We found that heat shock inhibited **p53** ubiquitination and caused accumulation of **p53** at the post-transcriptional level. Heat shock induced **phosphorylation** of **p53** at serine 15 in an **ATM** kinase-dependent fashion, which may contribute partially to heat-induced **p53** accumulation. However, **p53** accumulation also occurred after heat shock in **ATM**-deficient cells. Heat shock induced conformational change of wild type **p53** and **binding** to hsp90. Inhibition of hsp90-**p53** **interaction** by geldanamycin prevented **p53** accumulation partially in **ATM** -wild type cells and completely in **ATM**-deficient cells. Therefore, **phosphorylation** and **interaction** with hsp90 both contribute to stabilization of **p53** after heat shock.
ACCESSION NUMBER: 2003:123864 BIOSIS
DOCUMENT NUMBER: PREV200300123864
TITLE: **Phosphorylation** and hsp90 **binding** mediate heat shock stabilization of **p53**.
AUTHOR(S): Wang, Chuangui; Chen, Jiandong [Reprint Author]
CORPORATE SOURCE: H. Lee Moffitt Cancer Center, 12902 Magnolia Dr., MRC3057A, Tampa, FL, 33612, USA
jchen@moffitt.usf.edu
SOURCE: Journal of Biological Chemistry, (January 17 2003) Vol. 278, No. 3, pp. 2066-2071. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Mar 2003
Last Updated on STN: 5 Mar 2003

L8 ANSWER 20 OF 44 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
TI Kinetochore localisation of the DNA damage response component 53BP1 during mitosis.
AB 53BP1 is a vertebrate BRCT motif protein, originally described as a direct **interactor** of **p53**, which has recently been shown to be implicated in the early response to DNA damage. Upon DNA damage, 53BP1 re-localises to discrete nuclear foci that are thought to represent sites of DNA lesions and becomes hyper-phosphorylated. Several observations suggest that 53BP1 is a direct substrate for the ataxia telangiectasia mutated (**ATM**) kinase. So far, 53BP1 behaviour during mitosis has not been reported in detail. We have examined 53BP1 subcellular distribution in mitotic cells using several antibodies against 53BP1, and ectopic expression of GFP-tagged 53BP1. We found that 53BP1 significantly colocalised with CENP-E to kinetochores. 53BP1 is loaded to kinetochores in prophase, before CENP-E, and is released by mid-anaphase. By expressing various GFP-tagged 53BP1 truncations, the kinetochore **binding** domain has been mapped to a 380 residue portion of the protein the excludes the nuclear localisation signal and the BRCT motifs. Like many kinetochore-associated proteins involved in mitotic checkpoint signalling, more 53BP1 appears to accumulate on the kinetochores of chromosomes not aligned on the metaphase plate. Finally, we show that 53BP1 is hyperphosphorylated in mitotic cells, and undergoes an even higher level of **phosphorylation** in response to spindle disruption with colcemid. Our data suggest that 53BP1 may have a role in checkpoint signalling during mitosis and provide the evidence that DNA damage response machinery and mitotic checkpoint may share common molecular components.

ACCESSION NUMBER: 2002:141834 BIOSIS
DOCUMENT NUMBER: PREV200200141834
TITLE: Kinetochore localisation of the DNA damage response component 53BP1 during mitosis.
AUTHOR(S): Jullien, Denis; Vagnarelli, Paola; Earnshaw, William C.; Adachi, Yasuhisa [Reprint author]
CORPORATE SOURCE: The Wellcome Trust Centre for Cell Biology, Institute of Cell and Molecular Biology, The University of Edinburgh, King's Buildings, Edinburgh, EH9 3JR, UK
y.adachi@ed.ac.uk
SOURCE: Journal of Cell Science, (January 1, 2002) Vol. 115, No. 1, pp. 71-79. print.
CODEN: JNCSAI. ISSN: 0021-9533.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Feb 2002
Last Updated on STN: 26 Feb 2002

L8 ANSWER 21 OF 44 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
TI Replication-mediated DNA damage by camptothecin induces **phosphorylation** of RPA by DNA-dependent protein kinase and dissociates RPA:DNA-PK complexes.
AB Replication protein A (RPA) is a DNA single-strand **binding** protein essential for DNA replication, recombination and repair. In human cells treated with the topoisomerase inhibitors camptothecin or etoposide (VP-16), we find that RPA2, the middle-sized subunit of RPA, becomes rapidly phosphorylated. This response appears to be due to DNA-dependent protein kinase (DNA-PK) and to be independent of **p53** or the ataxia telangiectasia mutated (**ATM**) protein. RPA2 **phosphorylation** in response to camptothecin required ongoing DNA replication. Camptothecin itself partially inhibited DNA synthesis, and this inhibition followed the same kinetics as DNA-PK activation and RPA2 **phosphorylation**. DNA-PK activation and RPA2 **phosphorylation** were prevented by the cell-cycle checkpoint abrogator 7-hydroxystaurosporine (UCN01), which markedly potentiates camptothecin cytotoxicity. The DNA-PK catalytic subunit (DNA-PKcs) was found to bind RPA which was replaced by the Ku autoantigen upon camptothecin treatment. DNAPKcs **interacted** directly with RPA1 in vitro. We propose that the encounter of a replication fork with a topoisomerase-DNA cleavage complex could lead to a juxtaposition of replication fork-associated RPA and DNA double-strand end-associated DNA-PK, leading to RPA2 **phosphorylation** which may signal the presence of DNA damage to an S-phase checkpoint mechanism.
ACCESSION NUMBER: 1999:203571 BIOSIS
DOCUMENT NUMBER: PREV199900203571
TITLE: Replication-mediated DNA damage by camptothecin induces **phosphorylation** of RPA by DNA-dependent protein kinase and dissociates RPA:DNA-PK complexes.
AUTHOR(S): Shao, Rong-Guang; Cao, Chun-Xia; Zhang, Hongliang; Kohn, Kurt W.; Wold, Marc S.; Pommier, Yves [Reprint author]
CORPORATE SOURCE: Laboratory of Molecular Pharmacology, Division of Basic Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892-4255, USA
SOURCE: EMBO (European Molecular Biology Organization) Journal, (March, 1999) Vol. 18, No. 5, pp. 1397-1406. print.
CODEN: EMJODG. ISSN: 0261-4189.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 May 1999
Last Updated on STN: 26 May 1999

L8 ANSWER 22 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer,

immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR

AN AAW84272 Protein DGENE

AB The present sequence represents a human DNA-dependent protein kinase catalytic subunit (DNAPKcs) protein. The protein is used in the course of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.

ACCESSION NUMBER: AAW84272 Protein DGENE

TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR

INVENTOR: Jackson S P; Lakin N D; Smith G C M

PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.

PATENT INFO: GB 2327498 A 19990127 124p

APPLICATION INFO: GB 1998-15423 19980716

PRIORITY INFO: GB 1997-14971 19970716

DOCUMENT TYPE: Patent

LANGUAGE: English

OTHER SOURCE: 1999-073587 [07]

CROSS REFERENCES: N-PSDB: AAX04535

DESCRIPTION: A DNA-dependent protein kinase catalytic subunit.

L8 ANSWER 23 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN

TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR

AN AAW84271 Protein DGENE

AB The present sequence represents a human ATR (FRP1) protein. The protein is used in the course of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.

ACCESSION NUMBER: AAW84271 Protein DGENE

TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR

INVENTOR: Jackson S P; Lakin N D; Smith G C M

PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.

PATENT INFO: GB 2327498 A 19990127 124p

APPLICATION INFO: GB 1998-15423 19980716
PRIORITY INFO: GB 1997-14971 19970716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-073587 [07]
CROSS REFERENCES: N-PSDB: AAX04534
DESCRIPTION: A human ATR protein.

L8 ANSWER 24 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
AN AAW84270 Protein DGENE
AB The present sequence represents a human **p53** protein. The protein is used in the assay of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.
ACCESSION NUMBER: AAW84270 Protein DGENE
TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.
PATENT INFO: GB 2327498 A 19990127 124p
APPLICATION INFO: GB 1998-15423 19980716
PRIORITY INFO: GB 1997-14971 19970716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-073587 [07]
CROSS REFERENCES: N-PSDB: AAX04533
DESCRIPTION: Human **p53** protein.

L8 ANSWER 25 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
AN AAW84269 Protein DGENE
AB The present sequence represents ataxia telangiectasia (**ATM**) protein. The protein is used in the assay of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy

involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.

ACCESSION NUMBER: AAW84269 Protein DGENE
TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.
PATENT INFO: GB 2327498 A 19990127 124p
APPLICATION INFO: GB 1998-15423 19980716
PRIORITY INFO: GB 1997-14971 19970716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-073587 [07]
CROSS REFERENCES: N-PSDB: AAX04532
DESCRIPTION: Human ataxia telangiectasia (**ATM**) protein.

L8 ANSWER 26 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
AN AAX04535 DNA DGENE
AB The present sequence encodes a human DNA-dependent protein kinase catalytic subunit (DNAPKcs) protein. The protein is used in the course of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.

ACCESSION NUMBER: AAX04535 DNA DGENE
TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.
PATENT INFO: GB 2327498 A 19990127 124p
APPLICATION INFO: GB 1998-15423 19980716
PRIORITY INFO: GB 1997-14971 19970716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-073587 [07]
CROSS REFERENCES: P-PSDB: AAW84272
DESCRIPTION: DNA encoding a DNA-dependent protein kinase catalytic subunit.

L8 ANSWER 27 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR

AN AAX04532 DNA DGENE
AB The present sequence encodes ataxia telangiectasia (**ATM**) protein. The protein is used in the assay of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.
ACCESSION NUMBER: AAX04532 DNA DGENE
TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.
PATENT INFO: GB 2327498 A 19990127 124p
APPLICATION INFO: GB 1998-15423 19980716
PRIORITY INFO: GB 1997-14971 19970716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-073587 [07]
CROSS REFERENCES: P-PSDB: AAW84269
DESCRIPTION: DNA encoding human ataxia telangiectasia (**ATM**) protein.

L8 ANSWER 28 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
AN AAX04549 DNA DGENE
AB The present oligonucleotide was annealed with AAX04545, bound to streptavidin-coated iron oxide particles, and used in a protein purification method for **ATM**. The ataxia telangiectasia (**ATM**) protein is used in the assay of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.
ACCESSION NUMBER: AAX04549 DNA DGENE
TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
INVENTOR: Jackson S P; Lakin N D; Smith G C M

PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.
PATENT INFO: GB 2327498 A 19990127 124p
APPLICATION INFO: GB 1998-15423 19980716
PRIORITY INFO: GB 1997-14971 19970716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-073587 [07]
DESCRIPTION: Oligonucleotide DAM6 used to purify **ATM** protein.

L8 ANSWER 29 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
AN AAX04548 DNA DGENE
AB The present oligonucleotide was annealed with AAX04545 and AAX04547, bound to streptavidin-coated iron oxide particles, and used in a protein purification method for **ATM**. The ataxia telangiectasia (**ATM**) protein is used in the assay of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.
ACCESSION NUMBER: AAX04548 DNA DGENE
TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.
PATENT INFO: GB 2327498 A 19990127 124p
APPLICATION INFO: GB 1998-15423 19980716
PRIORITY INFO: GB 1997-14971 19970716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-073587 [07]
DESCRIPTION: Oligonucleotide DAM5 used to purify **ATM** protein.

L8 ANSWER 30 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
AN AAX04547 DNA DGENE
AB Oligonucleotides AAX04545-47 were annealed together, bound to streptavidin-coated iron oxide particles, and used in a protein purification method for **ATM**. The ataxia telangiectasia (**ATM**) protein is used in the assay of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction**

or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.

ACCESSION NUMBER: AAX04547 DNA DGENE
TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.
PATENT INFO: GB 2327498 A 19990127 124p
APPLICATION INFO: GB 1998-15423 19980716
PRIORITY INFO: GB 1997-14971 19970716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-073587 [07]
DESCRIPTION: Oligonucleotide DAM3 used to purify **ATM** protein.

L8 ANSWER 31 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
AN AAX04546 DNA DGENE
AB Oligonucleotides AAX04545-47 were annealed together, bound to streptavidin-coated iron oxide particles, and used in a protein purification method for **ATM**. The ataxia telangiectasia (**ATM**) protein is used in the assay of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.

ACCESSION NUMBER: AAX04546 DNA DGENE
TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.
PATENT INFO: GB 2327498 A 19990127 124p
APPLICATION INFO: GB 1998-15423 19980716
PRIORITY INFO: GB 1997-14971 19970716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-073587 [07]
DESCRIPTION: Oligonucleotide DAM2 used to purify **ATM** protein.

L8 ANSWER 32 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of

ATM and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR

AN AAX04545 DNA DGENE

AB Oligonucleotides AAX04545-47 were annealed together, bound to streptavidin-coated iron oxide particles, and used in a protein purification method for **ATM**. The ataxia telangiectasia (**ATM**) protein is used in the assay of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.

ACCESSION NUMBER: AAX04545 DNA DGENE

TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR

INVENTOR: Jackson S P; Lakin N D; Smith G C M

PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.

PATENT INFO: GB 2327498 A 19990127 124p

APPLICATION INFO: GB 1998-15423 19980716

PRIORITY INFO: GB 1997-14971 19970716

DOCUMENT TYPE: Patent

LANGUAGE: English

OTHER SOURCE: 1999-073587 [07]

DESCRIPTION: Oligonucleotide DYNO used to purify **ATM** protein.

L8 ANSWER 33 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN

TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR

AN AAX04544 DNA DGENE

AB The present oligonucleotides was bound to streptavidin-coated iron oxide particles, and used in a protein purification method for **ATM**. The ataxia telangiectasia (**ATM**) protein is used in the assay of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.

ACCESSION NUMBER: AAX04544 DNA DGENE

TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for

the purification of the proteins **ATM** and ATR
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.
PATENT INFO: GB 2327498 A 19990127 124p
APPLICATION INFO: GB 1998-15423 19980716
PRIORITY INFO: GB 1997-14971 19970716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-073587 [07]
DESCRIPTION: Oligonucleotide used to purify **ATM** protein.

L8 ANSWER 34 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
AN AAX04543 DNA DGENE
AB Oligonucleotides AAX04542-43 were annealed together, bound to streptavidin-coated iron oxide particles, and used in a protein purification method for **ATM**. The ataxia telangiectasia (**ATM**) protein is used in the assay of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.
ACCESSION NUMBER: AAX04543 DNA DGENE
TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.
PATENT INFO: GB 2327498 A 19990127 124p
APPLICATION INFO: GB 1998-15423 19980716
PRIORITY INFO: GB 1997-14971 19970716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-073587 [07]
DESCRIPTION: Oligonucleotide used to purify **ATM** protein.

L8 ANSWER 35 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
AN AAX04542 DNA DGENE
AB Oligonucleotides AAX04542-43 were annealed together, bound to streptavidin-coated iron oxide particles, and used in a protein purification method for **ATM**. The ataxia telangiectasia (**ATM**) protein is used in the assay of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises

contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.

ACCESSION NUMBER: AAX04542 DNA DGENE
TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.
PATENT INFO: GB 2327498 A 19990127 124p
APPLICATION INFO: GB 1998-15423 19980716
PRIORITY INFO: GB 1997-14971 19970716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-073587 [07]
DESCRIPTION: Oligonucleotide used to purify **ATM** protein.

L8 ANSWER 36 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
AN AAX04541 DNA DGENE
AB Oligonucleotides AAX04540-41 were annealed together, bound to streptavidin-coated iron oxide particles, and used in a protein purification method for **ATM**. The ataxia telangiectasia (**ATM**) protein is used in the assay of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.

ACCESSION NUMBER: AAX04541 DNA DGENE
TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.
PATENT INFO: GB 2327498 A 19990127 124p
APPLICATION INFO: GB 1998-15423 19980716
PRIORITY INFO: GB 1997-14971 19970716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-073587 [07]
DESCRIPTION: Oligonucleotide used to purify **ATM** protein.

L8 ANSWER 37 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
AN AAX04540 DNA DGENE
AB Oligonucleotides AAX04540-41 were annealed together, bound to streptavidin-coated iron oxide particles, and used in a protein purification method for **ATM**. The ataxia telangiectasia (**ATM**) protein is used in the assay of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.
ACCESSION NUMBER: AAX04540 DNA DGENE
TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.
PATENT INFO: GB 2327498 A 19990127 124p
APPLICATION INFO: GB 1998-15423 19980716
PRIORITY INFO: GB 1997-14971 19970716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-073587 [07]
DESCRIPTION: Oligonucleotide used to purify **ATM** protein.

L8 ANSWER 38 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
AN AAX04539 DNA DGENE
AB Oligonucleotides AAX04538-39 were annealed together, bound to streptavidin-coated iron oxide particles, and used in a protein purification method for **ATM**. The ataxia telangiectasia (**ATM**) protein is used in the assay of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.
ACCESSION NUMBER: AAX04539 DNA DGENE

TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.
PATENT INFO: GB 2327498 A 19990127 124p
APPLICATION INFO: GB 1998-15423 19980716
PRIORITY INFO: GB 1997-14971 19970716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-073587 [07]
DESCRIPTION: Oligonucleotide used to purify **ATM** protein.

L8 ANSWER 39 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
AN AAX04538 DNA DGENE
AB Oligonucleotides AAX04538-39 were annealed together, bound to streptavidin-coated iron oxide particles, and used in a protein purification method for **ATM**. The ataxia telangiectasia (**ATM**) protein is used in the assay of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.
ACCESSION NUMBER: AAX04538 DNA DGENE
TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.
PATENT INFO: GB 2327498 A 19990127 124p
APPLICATION INFO: GB 1998-15423 19980716
PRIORITY INFO: GB 1997-14971 19970716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-073587 [07]
DESCRIPTION: Oligonucleotide used to purify **ATM** protein.

L8 ANSWER 40 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
AN AAX04537 DNA DGENE
AB Oligonucleotides AAX04536-37 were annealed together, bound to streptavidin-coated iron oxide particles, and used in a protein purification method for **ATM**. The ataxia telangiectasia (**ATM**) protein is used in the assay of the invention. The specification describes an assay method for a compound able to modulate

the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.

ACCESSION NUMBER: AAX04537 DNA DGENE
TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.
PATENT INFO: GB 2327498 A 19990127 124p
APPLICATION INFO: GB 1998-15423 19980716
PRIORITY INFO: GB 1997-14971 19970716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-073587 [07]
DESCRIPTION: Oligonucleotide used to purify **ATM** protein.

L8 ANSWER 41 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
AN AAX04536 DNA DGENE
AB Oligonucleotides AAX04536-37 were annealed together, bound to streptavidin-coated iron oxide particles, and used in a protein purification method for **ATM**. The ataxia telangiectasia (**ATM**) protein is used in the assay of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.

ACCESSION NUMBER: AAX04536 DNA DGENE
TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.
PATENT INFO: GB 2327498 A 19990127 124p
APPLICATION INFO: GB 1998-15423 19980716
PRIORITY INFO: GB 1997-14971 19970716
DOCUMENT TYPE: Patent
LANGUAGE: English

OTHER SOURCE: 1999-073587 [07]
DESCRIPTION: Oligonucleotide used to purify **ATM** protein.

L8 ANSWER 42 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
AN AAX04534 DNA DGENE
AB The present sequence encodes a human ATR (FRP1) protein. The protein is used in the course of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.
ACCESSION NUMBER: AAX04534 DNA DGENE
TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.
PATENT INFO: GB 2327498 A 19990127 124p
APPLICATION INFO: GB 1998-15423 19980716
PRIORITY INFO: GB 1997-14971 19970716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-073587 [07]
CROSS REFERENCES: P-PSDB: AAW84271
DESCRIPTION: DNA encoding human ATR protein.

L8 ANSWER 43 OF 44 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR
AN AAX04533 DNA DGENE
AB The present sequence encodes a human **p53** protein. The protein is used in the assay of the invention. The specification describes an assay method for a compound able to modulate the **interaction** between **ATM** or a protein having an associated kinase activity and **p53** or a protein having homologous **phosphorylation** sites. The assay comprises contacting a peptide fragment **ATM** with a relevant fragment of **p53** and a test compound, and determining the **interaction** or **binding** between the substances and the test compound. The assay method is useful for screening for compounds able to modulate the **interaction** between **ATM** and **p53**. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR.
ACCESSION NUMBER: AAX04533 DNA DGENE
TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment

of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR

INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (CANC-N)CANCER RES CAMPAIGN TECHNOLOGY.
PATENT INFO: GB 2327498 A 19990127 124p
APPLICATION INFO: GB 1998-15423 19980716
PRIORITY INFO: GB 1997-14971 19970716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-073587 [07]
CROSS REFERENCES: P-PSDB: AAW84270
DESCRIPTION: DNA encoding human **p53** protein.

L8 ANSWER 44 OF 44 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
TI Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR.
AN 1999-073587 [07] WPIDS
CR 2003-232383 [23]
AB GB 2327498 A UPAB: 20030407
An assay method for a compound able to modulate the **interaction** between (i) **ATM** or a protein having an associated kinase activity and (ii) **p53** or a protein having homologous **phosphorylation** sites is claimed, comprising contacting a peptide fragment or derivative or analogue of (i) with a relevant fragment of **p53** or its homologue and a test compound, and determining the **interaction** or **binding** between the substances and the test compound.

USE - The assay method is useful for screening for compounds able to modulate the **interaction** between (i) **ATM** or a protein with associated kinase activity and (ii) **p53** or a protein having homologous **phosphorylation** sites. The screened agents, peptide fragments and nucleic acids are useful for therapy involving modulating **ATM** action e.g. in the treatment of cancer, immunosuppression or HIV infections by modulating **phosphorylation** of **p53** by **ATM**, and for purifying the proteins **ATM** and ATR (claimed).

ADVANTAGE - **ATM** is shown to bind DNA and phosphorylate **p53** at the Ser 15 and Thr 18 positions.

Dwg.0/32

ACCESSION NUMBER: 1999-073587 [07] WPIDS
CROSS REFERENCE: 2003-232383 [23]
DOC. NO. CPI: C1999-022059
TITLE: Assay method for compounds modulating the **interaction** of **ATM** and **p53** - useful for the treatment of e.g. cancer, immunosuppression and HIV infections and for the purification of the proteins **ATM** and ATR.
DERWENT CLASS: B04 D16
INVENTOR(S): JACKSON, S P; LAKIN, N D; SMITH, G C M; HANN, B; LANE, D P
PATENT ASSIGNEE(S): (KUDO-N) KUDOS PHARM LTD; (CANC-N) CANCER RES CAMPAIGN TECHNOLOGY
COUNTRY COUNT: 83
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
GB 2327498	A	19990127	(199907)*		124
WO 9904266	A2	19990128	(199911)	EN	

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE

GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG
US UZ VN YU ZW

AU 9884492 A 19990210 (199925)
EP 996858 A2 20000503 (200026) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 2001510684 W 20010807 (200150) 209
GB 2327498 B 20020410 (200232)
AU 747594 B 20020516 (200244)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
GB 2327498	A	GB 1998-15423	19980716
WO 9904266	A2	WO 1998-GB2115	19980716
AU 9884492	A	AU 1998-84492	19980716
EP 996858	A2	EP 1998-935132	19980716
		WO 1998-GB2115	19980716
JP 2001510684	W	WO 1998-GB2115	19980716
		JP 2000-503426	19980716
GB 2327498	B	GB 1998-15423	19980716
AU 747594	B	AU 1998-84492	19980716

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9884492	A	Based on	WO 9904266
EP 996858	A2	Based on	WO 9904266
JP 2001510684	W	Based on	WO 9904266
AU 747594	B	Previous Publ.	AU 9884492
		Based on	WO 9904266

PRIORITY APPLN. INFO: GB 1997-14971 19970716

=> d his

(FILE 'HOME' ENTERED AT 16:51:28 ON 22 APR 2004)

FILE 'MEDLINE, BIOSIS, DGENE, FSTA, WPIDS' ENTERED AT 16:51:57 ON 22 APR 2004

L1 0 S P53 () INTERACT? () ATM
L2 948 S ATM AND P53
L3 126 S L2 AND INTERACT?
L4 185 S L2 AND BINDING
L5 61 S L4 AND L3
L6 2 S L5 AND BINDING ASSAY
L7 0 S L5 AND MDM-2
L8 44 S L5 AND PHOSPHORYLATION

=> s Mdm2
L9 5807 MDM2

=> s l9 and l5
L10 7 L9 AND L5

=> d l10 ti abs ibib tot

L10 ANSWER 1 OF 7 MEDLINE on STN
TI Electron microscopy and 3D reconstructions reveal that human **ATM** kinase uses an arm-like domain to clamp around double-stranded DNA.
AB The human tumor suppressor gene ataxia telangiectasia mutated (**ATM**

) encodes a 3056 amino-acid protein kinase that regulates cell cycle checkpoints. **ATM** is defective in the neurodegenerative and cancer predisposition syndrome ataxia-telangiectasia. **ATM** protein kinase is activated by DNA damage and responds by phosphorylating downstream effectors involved in cell cycle arrest and DNA repair, such as **p53**, **MDM2**, CHEK2, BRCA1 and H2AX. **ATM** is probably a component of, or in close proximity to, the double-stranded DNA break-sensing machinery. We have observed purified human **ATM** protein, **ATM**-DNA and **ATM**-DNA-avidin bound complexes by single-particle electron microscopy and obtained three-dimensional reconstructions which show that **ATM** is composed of two main domains comprising a head and an arm. DNA **binding** to **ATM** induces a large conformational movement of the arm-like domain. Taken together, these three structures suggest that **ATM** is capable of **interacting** with DNA, using its arm to clamp around the double helix.

ACCESSION NUMBER: 2003292988 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12813460
TITLE: Electron microscopy and 3D reconstructions reveal that human **ATM** kinase uses an arm-like domain to clamp around double-stranded DNA.
AUTHOR: Llorca O; Rivera-Calzada A; Grantham J; Willison K R
CORPORATE SOURCE: The Institute of Cancer Research, Cancer Research UK, Center for Cell and Molecular Biology, Chester Beatty Laboratories, 237 Fulham Road, London SW3 6JB, UK.
SOURCE: Oncogene, (2003 Jun 19) 22 (25) 3867-74. Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030625
Last Updated on STN: 20030725
Entered Medline: 20030724

L10 ANSWER 2 OF 7 MEDLINE on STN
TI Critical roles for the serine 20, but not the serine 15, phosphorylation site and for the polyproline domain in regulating **p53** turnover.
AB The **p53** tumour suppressor protein is a short-lived transcription factor that becomes stabilized in response to a wide range of cellular stresses. Ubiquitination and the targeting of **p53** for degradation by the proteasome are mediated by **Mdm2** (mouse double minute clone 2), a negative regulatory partner of **p53**. Previous studies have suggested that DNA-damage-induced phosphorylation of **p53** at key N-terminal sites has a pivotal role in regulating the **interaction** with **Mdm2** but the precise role of phosphorylation of serines 15 and 20 is still unclear. Here we show that replacement of serine 15 and a range of other key N-terminal phosphorylation sites with alanine, which cannot be phosphorylated, has little effect on the ubiquitination and degradation of full-length human **p53**. In contrast, replacement of serine 20 makes **p53** highly sensitive to **Mdm2**-mediated turnover. These results define distinct roles for serines 15 and 20, two sites previously demonstrated to be dependent on phosphorylation through mechanisms mediated by DNA damage and **ATM** (ataxia telangiectasia mutated). We also show that the polyproline region of **p53**, a domain that has a key role in **p53**-induced apoptosis, exerts a critical influence over the **Mdm2**-mediated turnover of **p53**.

ACCESSION NUMBER: 2001536345 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11583595
TITLE: Critical roles for the serine 20, but not the serine 15, phosphorylation site and for the polyproline domain in regulating **p53** turnover.

AUTHOR: Dumaz N; Milne D M; Jardine L J; Meek D W
CORPORATE SOURCE: Biomedical Research Centre, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, UK.
SOURCE: Biochemical journal, (2001 Oct 15) 359 (Pt 2) 459-64. Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011004
Last Updated on STN: 20020420
Entered Medline: 20011204

L10 ANSWER 3 OF 7 MEDLINE on STN
TI Phosphorylation of Ser-20 mediates stabilization of human **p53** in response to DNA damage.
AB Stabilization of **p53** in response to DNA damage is caused by its dissociation from **Mdm2**, a protein that targets **p53** for degradation in the proteasome. Dissociation of **p53** from **Mdm2** could be caused by DNA damage-induced **p53** posttranslational modifications. The **ATM** and ATR kinases, whose activation in response to ionizing radiation (IR) and UV light, respectively, is required for **p53** stabilization, directly phosphorylate **p53** on Ser-15. However, phosphorylation of Ser-15 is critical for the apoptotic activity of **p53** and not for **p53** stabilization. Thus, whether any **p53** modifications, and which, underlie disruption of the **p53-Mdm2** complex after DNA damage remains to be determined. We analyzed the IR- and UV light-induced stabilization of **p53** proteins with substitutions of Ser known to be posttranslationally modified after DNA damage. Substitution of Ser-20 was sufficient to abrogate **p53** stabilization in response to both IR and UV light. Furthermore, both IR and UV light induced phosphorylation of **p53** on Ser-20, which involved the majority of nuclear **p53** protein and weakened the **interaction** of **p53** with **Mdm2** in vitro. **ATM** and ATR cannot phosphorylate **p53** on Ser-20. We therefore propose that **ATM** and ATR activate an, as yet unidentified, kinase that stabilizes **p53** by phosphorylating it on Ser-20.
ACCESSION NUMBER: 2000040627 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10570149
TITLE: Phosphorylation of Ser-20 mediates stabilization of human **p53** in response to DNA damage.
AUTHOR: Chehab N H; Malikzay A; Stavridi E S; Halazonetis T D
CORPORATE SOURCE: Department of Molecular Genetics, The Wistar Institute, Philadelphia, PA 19104, USA.
CONTRACT NUMBER: CA76367 (NCI)
T32 CA09171 (NCI)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1999 Nov 23) 96 (24) 13777-82. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000114
Last Updated on STN: 20000114
Entered Medline: 20000106

L10 ANSWER 4 OF 7 MEDLINE on STN
TI DNA damage induced **p53** stabilization: no indication for an involvement of **p53** phosphorylation.

AB Abundance and activity of **p53** are predominantly regulated posttranslationally. Structural disturbance in transcribed genes induced by radiation, e.g. DNA damage, or by transcriptional inhibitors cause **p53** protein stabilization by a yet unknown mechanism. Using stable and transient transfections for the analysis of **p53** mutant proteins, we have ruled out a role in stabilization by UV, gamma irradiation or actinomycin C for the following putative phosphorylation sites in the **p53** protein: serines 6, 9, 15, 33, 315 and 392, and threonine 18. By double mutation combinations of phosphorylations were also ruled out; 6,9; 15,18; 15,37. These mutations eliminate modifications by casein kinases I and II, DNA-PK, **ATM**, CDK and JNK. Also the 30 carboxyterminal amino acids are not required for induced **p53** stabilization. Thus neither phosphorylations of individual amino acids nor **interactions** of the carboxyterminus of **p53** with cellular macromolecules appear to play a role in the stabilization process. The only single prerequisite for induced stabilization of **p53** is its prior destabilization by **Mdm2**. However, the level of active **Mdm2** must be controlled carefully: overexpression of **Mdm2** inhibits UV induced **p53** stabilization.

ACCESSION NUMBER:	1999223132 MEDLINE
DOCUMENT NUMBER:	PubMed ID: 10208433
TITLE:	DNA damage induced **p53** stabilization: no indication for an involvement of **p53** phosphorylation.
AUTHOR:	Blattner C; Tobiasch E; Litfen M; Rahmsdorf H J; Herrlich P
CORPORATE SOURCE:	Forschungszentrum Karlsruhe, Institut fur Genetik, Universitat Karlsruhe, Germany.
SOURCE:	Oncogene, (1999 Mar 4) 18 (9) 1723-32. Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY:	ENGLAND: United Kingdom
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	199906
ENTRY DATE:	Entered STN: 19990614 Last Updated on STN: 19990614 Entered Medline: 19990601

L10 ANSWER 5 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

TI Molecular Mechanisms Mediating Anti-Myeloma Activity of Proteasome Inhibitor PS-341.

AB PS-341 (pyrazylcarbonyl-Phe-Leu-boronate) is a peptide boronate proteasome inhibitors which induces apoptosis in drug resistant multiple myeloma (MM) cells, inhibits **binding** of MM cells in the bone marrow microenvironment, and inhibits cytokines mediating MM cell growth, survival, drug resistance, and migration in vitro. Moreover, PS-341 also inhibits human MM cell growth and prolongs survival in a SCID mouse model. Most importantly, PS-341 has achieved responses, even complete responses, in a Phase II clinical trial treating patients with relapsed MM refractory to conventional therapies, and has an acceptable toxicity profile. In this study, we further defined the molecular mechanisms whereby PS-341 mediates anti-MM activity. PS-341 treatment (20 nM, up to 16 h incubation) transiently upregulates **p53** protein expression in MM.1S cells, with peak expression at 8 h. PS-341 also induces transient **p53** phosphorylation on serine 15 (Ser15), without phosphorylation of Ser 6, 9, 20, 37, 46, or 392 residues. **MDM2** protein is similarly transiently upregulated after PS-341 treatment, with peak protein expression observed at 6 h. Importantly, PS-341 also induces phosphorylation (Ser15) and upregulation of **p53** and **MDM2** protein expression in freshly isolated patient MM cells. These results suggest that PS-341 induces DNA damage in both MM cell lines and patient MM cells. We demonstrated that PS-341 induces co-immunoprecipitation of **p53** with c-Jun NH2-terminal kinase (JNK) in a time-dependent

fashion; phosphorylation of JNK, as well as both upstream (SEK-1) and down stream (c-Jun and ATF-2) proteins; as well as significant (2.5 - 72 fold) increase in heat shock proteins transcription in a time-dependent fashion, assessed by gene microarray. These results indicate that PS-341 induces a stress response, as well as **interaction** of **p53** and JNK, in MM cell lines. The JNK specific inhibitor SP600125 blocks phosphorylation of JNK triggered by PS-341 in a dose-dependent fashion; and PS-341-induced cytotoxicity in MM.1S cells, without blocking PS-341-induced **p53** phosphorylation or induction of **MDM2** . These results suggest that signaling between **p53** and JNK is through **p53** to JNK, but not via JNK to **p53**, and that JNK plays a critical role in mediating PS-341-induced apoptosis via activation of caspase-3. Most importantly, PS-341 cleaves DNA-PKcs and **ATM** in a time-, and dose-dependent fashion in MM cell lines, as well as patient's MM cells suggesting that PS-341 impairs DNA repair. Pan-caspase inhibitor Z-VAD-FMK and caspase-8 inhibitor Z-IETD-FMK completely abrogate DNA-PKcs and **ATM** cleavage induced by PS-341. These results suggest that PS-341 induces: DNA-PKcs and **ATM** cleavage; phosphorylation of **p53** and **MDM2** cleavage via caspase-3 activation; and **ATM** or ATR activation by activation of caspase-3 via caspase-8. Given the early clinical promise of and favorable toxicity profile of PS-341 in patients with relapsed refractory MM, these studies provide the framework for further clinical evaluation of PS-341, alone and coupled with conventional or other novel therapies, to improve patient outcome in MM.

ACCESSION NUMBER: 2003:357350 BIOSIS
DOCUMENT NUMBER: PREV200300357350
TITLE: Molecular Mechanisms Mediating Anti-Myeloma Activity of Proteasome Inhibitor PS-341.
AUTHOR(S): Hideshima, Teru [Reprint Author]; Mitsiades, Constantine [Reprint Author]; Akiyama, Masaharu [Reprint Author]; Hayashi, Toshiaki [Reprint Author]; Chauhan, Dharminder [Reprint Author]; Richardson, Paul G. [Reprint Author]; Schlossman, Robert L. [Reprint Author]; Podar, Klaus [Reprint Author]; Munshi, Nikhil C. [Reprint Author]; Mitsiades, Nicholas [Reprint Author]; Anderson, Kenneth C. [Reprint Author]
CORPORATE SOURCE: Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Boston, MA, USA
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 3215. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Aug 2003
Last Updated on STN: 6 Aug 2003

L10 ANSWER 6 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
TI Correlation of Interphase Fluorescence In Situ Hybridization (FISH) Anomalies with Cell Morphology and Immunophenotyping in Chronic Lymphocytic Leukemia (B-CLL).
AB Chromosomal anomalies detected by interphase FISH are among the most important factors predicting survival in B-CLL. These same FISH anomalies may also be associated with other biological features of B-CLL such as antigen expression on leukemic B-lymphocytes and cell morphology. Thus, we studied peripheral blood from 107 patients (pts) at enrollment in ECOG's randomized phase III trial E2997 (fludarabine and cyclophosphamide versus fludarabine). Pts were required to have B-CLL and require therapy as defined by NCI criteria. FISH anomalies detected and sets of probes were 6q- (c-MYB, 6q23 and D6Z1, CEN6), 11q- (**ATM**, 11q23 and

D11Z1, CEN11), 13q- (D13S319, 13q14 and D13S327, 13q34), 17p- (**P53**, 17p13.1 and D17Z1, CEN17), +12 (D12Z3, CEN12 and **MDM2**, 12q15), and translocations of CCND1 at 11q13 and/or IgH at 14q32. A total of 89 (83%) pts were abnormal by FISH: 62 (70%) had a single anomaly, 23 (26%) had two and 4 (4%) had gtoreq3. Among 121 FISH anomalies detected, 13q- was most frequent (46%) followed by +12 (19%), 11q- (18%), 17p- (7%), 6q- (5%) and translocations of IgH (4%). Five pts had gtoreq3 IgH signals: one had CCND1/IgH fusion suggesting a t(11;14)(q13;q32); the other four had extra IgH signals of unknown origin. To establish genetic subgroups, we followed the hierarchical risk model of FISH anomalies in B-CLL defined by Dohner et al (NEJM 343:1910, 2000): worst prognosis 17p- (8 pts) fwdarw 11q- (21 pts) fwdarw 6q- (5 pts) fwdarw +12 (20 pts) fwdarw normal (18 pts) fwdarw best prognosis 13q- (35 pts). A general linear model was used to estimate the relationship between FISH anomalies, marker profile and cell morphology (atypical vs typical). Immunophenotypic indicators monitored were percent leukemic cells expressing CD38, CD23, CD20, CD22, CD5, CD25, CD11c, surface CD79a, surface CD79b, FMC7, CD11a, CD15, CD18, P-glycoprotein and mean fluorescence intensity (MFI) of CD38, CD23, CD22, CD5, surface CD79b, CD18 **binding**. No significant association was apparent between FISH results and cell morphology (p=0.21). Atypical morphology was associated with a higher MFI of CD79b expression, the Igbeta domain of the B-cell antigen receptor (BCR) (p<0.05). Trisomy 12 showed a unique immunologic fingerprint with high percentage of cells expressing CD38 (ecto-enzyme involved in cell-cell **interactions**), CD79a (Igalpha domain of BCR) and CD11c (alphaX integrin), and high MFI for the adhesion molecule CD22 (p<0.05). CD38, a known prognostic marker in B-CLL, was lowest in pts with 13q- and highest among pts with +12 (p<0.05). This as yet unappreciated concordance between antigen profile and FISH anomalies in B-CLL will be validated in future pts entered on E2997 and may lead to a new classification system for B-CLL. This work was supported by NIH/R01 CA-88647.

ACCESSION NUMBER: 2003:337032 BIOSIS
DOCUMENT NUMBER: PREV200300337032
TITLE: Correlation of Interphase Fluorescence In Situ Hybridization (FISH) Anomalies with Cell Morphology and Immunophenotyping in Chronic Lymphocytic Leukemia (B-CLL).
AUTHOR(S): Dewald, Gordon W. [Reprint Author]; Paietta, Elisabeth [Reprint Author]; Goloubeva, Olga [Reprint Author]; Bennett, John M. [Reprint Author]; Brockman, Stephanie R.; Paternoster, Sarah F.; Lucas, David; Neuberg, Donna [Reprint Author]; Flinn, Ian [Reprint Author]; Tallman, Martin [Reprint Author]; Grever, Michael [Reprint Author]; Byrd, John
CORPORATE SOURCE: Eastern Cooperative Oncology Group, Boston, MA, USA
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 2334. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Jul 2003
Last Updated on STN: 23 Jul 2003

L10 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
TI Electron microscopy and 3D reconstructions reveal that human **ATM** kinase uses an arm-like domain to clamp around double-stranded DNA.
AB The human tumor suppressor gene ataxia telangiectasia mutated (**ATM**) encodes a 3056 amino-acid protein kinase that regulates cell cycle checkpoints. **ATM** is defective in the neurodegenerative and cancer predisposition syndrome ataxia-telangiectasia. **ATM**

protein kinase is activated by DNA damage and responds by phosphorylating downstream effectors involved in cell cycle arrest and DNA repair, such as **p53**, **MDM2**, CHEK2, BRCA1 and H2AX. **ATM** is probably a component of, or in close proximity to, the double-stranded DNA break-sensing machinery. We have observed purified human **ATM** protein, **ATM**-DNA and **ATM**-DNA-avidin bound complexes by single-particle electron microscopy and obtained three-dimensional reconstructions which show that **ATM** is composed of two main domains comprising a head and an arm. DNA **binding** to **ATM** induces a large conformational movement of the arm-like domain. Taken together, these three structures suggest that **ATM** is capable of **interacting** with DNA, using its arm to clamp around the double helix.

ACCESSION NUMBER: 2003:323935 BIOSIS
DOCUMENT NUMBER: PREV200300323935
TITLE: Electron microscopy and 3D reconstructions reveal that human **ATM** kinase uses an arm-like domain to clamp around double-stranded DNA.
AUTHOR(S): Llorca, O.; Rivera-Calzada, A.; Grantham, J.; Willison, K. R. [Reprint Author]
CORPORATE SOURCE: Center for Cell and Molecular Biology, Chester Beatty Laboratories, Institute of Cancer Research, Cancer Research UK, 237 Fulham Road, London, SW3 6JB, UK
Keith.Willison@icr.ac.uk
SOURCE: Oncogene, (19 June 2003) Vol. 22, No. 25, pp. 3867-3874. print.
ISSN: 0950-9232 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Jul 2003
Last Updated on STN: 16 Jul 2003

=> d his

(FILE 'HOME' ENTERED AT 16:51:28 ON 22 APR 2004)

FILE 'MEDLINE, BIOSIS, DGENE, FSTA, WPIDS' ENTERED AT 16:51:57 ON 22 APR 2004

```
L1            0 S P53 () INTERACT? () ATM
L2          948 S ATM  AND P53
L3          126 S L2 AND INTERACT?
L4          185 S L2 AND BINDING
L5           61 S L4 AND L3
L6            2 S L5 AND BINDING ASSAY
L7            0 S L5 AND MDM-2
L8           44 S L5 AND PHOSPHORYLATION
L9         5807 S  MDM2
L10           7 S L9 AND L5

=> s l8 and ser15
L11           1 L8 AND SER15

=> d l11 ti abs ibib tot

L11  ANSWER 1 OF 1  BIOSIS  COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
TI   Molecular Mechanisms Mediating Anti-Myeloma Activity of Proteasome
     Inhibitor PS-341.
AB   PS-341 (pyrazylcarbonyl-Phe-Leu-boronate) is a peptide boronate proteasome
     inhibitors which induces apoptosis in drug resistant multiple myeloma (MM)
     cells, inhibits binding of MM cells in the bone marrow
     microenvironment, and inhibits cytokines mediating MM cell growth,
     survival, drug resistance, and migration in vitro.  Moreover, PS-341 also
     inhibits human MM cell growth and prolongs survival in a SCID mouse model.
```

Most importantly, PS-341 has achieved responses, even complete responses, in a Phase II clinical trial treating patients with relapsed MM refractory to conventional therapies, and has an acceptable toxicity profile. In this study, we further defined the molecular mechanisms whereby PS-341 mediates anti-MM activity. PS-341 treatment (20 nM, up to 16 h incubation) transiently upregulates **p53** protein expression in MM.1S cells, with peak expression at 8 h. PS-341 also induces transient **p53 phosphorylation** on serine 15 (**Ser15**), without **phosphorylation** of Ser 6, 9, 20, 37, 46, or 392 residues. MDM2 protein is similarly transiently upregulated after PS-341 treatment, with peak protein expression observed at 6 h. Importantly, PS-341 also induces **phosphorylation** (**Ser15**) and upregulation of **p53** and MDM2 protein expression in freshly isolated patient MM cells. These results suggest that PS-341 induces DNA damage in both MM cell lines and patient MM cells. We demonstrated that PS-341 induces co-immunoprecipitation of **p53** with c-Jun NH2-terminal kinase (JNK) in a time-dependent fashion; **phosphorylation** of JNK, as well as both upstream (SEK-1) and down stream (c-Jun and ATF-2) proteins; as well as significant (2.5 - 72 fold) increase in heat shock proteins transcription in a time-dependent fashion, assessed by gene microarray. These results indicate that PS-341 induces a stress response, as well as **interaction** of **p53** and JNK, in MM cell lines. The JNK specific inhibitor SP600125 blocks **phosphorylation** of JNK triggered by PS-341 in a dose-dependent fashion; and PS-341-induced cytotoxicity in MM.1S cells, without blocking PS-341-induced **p53 phosphorylation** or induction of MDM2. These results suggest that signaling between **p53** and JNK is through **p53** to JNK, but not via JNK to **p53**, and that JNK plays a critical role in mediating PS-341-induced apoptosis via activation of caspase-3. Most importantly, PS-341 cleaves DNA-PKcs and **ATM** in a time-, and dose-dependent fashion in MM cell lines, as well as patient's MM cells suggesting that PS-341 impairs DNA repair. Pan-caspase inhibitor Z-VAD-FMK and caspase-8 inhibitor Z-IETD-FMK completely abrogate DNA-PKcs and **ATM** cleavage induced by PS-341. These results suggest that PS-341 induces: DNA-PKcs and **ATM** cleavage; **phosphorylation** of **p53** and MDM2 cleavage via caspase-3 activation; and **ATM** or ATR activation by activation of caspase-3 via caspase-8. Given the early clinical promise of and favorable toxicity profile of PS-341 in patients with relapsed refractory MM, these studies provide the framework for further clinical evaluation of PS-341, alone and coupled with conventional or other novel therapies, to improve patient outcome in MM.

ACCESSION NUMBER: 2003:357350 BIOSIS
DOCUMENT NUMBER: PREV200300357350
TITLE: Molecular Mechanisms Mediating Anti-Myeloma Activity of Proteasome Inhibitor PS-341.
AUTHOR(S): Hideshima, Teru [Reprint Author]; Mitsiades, Constantine [Reprint Author]; Akiyama, Masaharu [Reprint Author]; Hayashi, Toshiaki [Reprint Author]; Chauhan, Dharminder [Reprint Author]; Richardson, Paul G. [Reprint Author]; Schlossman, Robert L. [Reprint Author]; Podar, Klaus [Reprint Author]; Munshi, Nikhil C. [Reprint Author]; Mitsiades, Nicholas [Reprint Author]; Anderson, Kenneth C. [Reprint Author]
CORPORATE SOURCE: Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Boston, MA, USA
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 3215. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English
ENTRY DATE: Entered STN: 6 Aug 2003
Last Updated on STN: 6 Aug 2003

=> d his

(FILE 'HOME' ENTERED AT 16:51:28 ON 22 APR 2004)

FILE 'MEDLINE, BIOSIS, DGENE, FSTA, WPIDS' ENTERED AT 16:51:57 ON 22 APR 2004

```
L1            0 S P53 () INTERACT? () ATM
L2          948 S ATM  AND P53
L3          126 S L2 AND INTERACT?
L4          185 S L2 AND BINDING
L5           61 S L4 AND L3
L6            2 S L5 AND BINDING ASSAY
L7            0 S L5 AND MDM-2
L8           44 S L5 AND PHOSPHORYLATION
L9         5807 S  MDM2
L10           7 S L9 AND L5
L11           1 S L8 AND SER15

=> s l8 and Thr18
L12           0 L8 AND THR18

=> s ATM and binding
L13         778 ATM AND BINDING

=> s p53 and binding
L14       13382 P53 AND BINDING

=> s l13 and l14
L15         186 L13 AND L14

=> s l15 and inhibit?
L16          91 L15 AND INHIBIT?

=> s l16 and assay
L17          24 L16 AND ASSAY

=> d l17 ti abs ibib tot

L17   ANSWER 1 OF 24  DGENE  COPYRIGHT 2004 THOMSON DERWENT on STN
TI    Assay for compound affecting DNA binding by
      ataxia-telangiectasia mutated gene, by bringing into contact the gene,
      protein with kinase activity, DNA and test compound, and determining
      binding of the gene and DNA  -
AN    ABP97122  Protein       DGENE
AB    The present invention describes an assay (M1) for a compound
      able to affect DNA binding by an ataxia-telangiectasia mutated
      (ATM) protein or a protein having an associated kinase
      activity. M1 comprises bringing into contact a substance which is
      ATM or a protein having an associated kinase activity which is
      able to bind DNA and a test compound, and determining binding
      of ATM and DNA in the presence of the test compound. Also
      described: (1) an agent (I) capable of affecting DNA binding by
      ATM obtained using M1; (2) purifying (M2) ATM or
      related kinase such as ATR; (3) use of DNA (II) for purifying ATM
      or ATR; and (4) a substantially pure ATM (III) or ATR (IV).
      ATM has anti-HIV, cytostatic, antipsoriatic and antitumour
      activities. M1 is useful for assaying for a compound able to affect DNA
      binding by ATM or a protein having an associated kinase
      activity. (I) is useful in therapy involving modulating ATM
```

action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence represents a human **p53** related peptide which is given in the exemplification of the present invention.

ACCESSION NUMBER: ABP97122 Protein DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N) KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
DESCRIPTION: Human **p53** related peptide.

L17 ANSWER 2 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
AN ABP97121 Protein DGENE
AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence represents human DNA dependent protein kinase catalytic subunit (DNA-PKcs) which is given in the exemplification of the present

invention.

ACCESSION NUMBER: ABP97121 Protein DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N) KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
CROSS REFERENCES: N-PSDB: ACC49402
DESCRIPTION: Human DNA dependent protein kinase catalytic subunit protein.

L17 ANSWER 3 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
AN ABP97120 Protein DGENE
AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence represents human ATR (also known as FRAP-related protein FRP1) which is given in the exemplification of the present invention.
ACCESSION NUMBER: ABP97120 Protein DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N) KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716

GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
CROSS REFERENCES: N-PSDB: ACC49401
DESCRIPTION: Human ATR (FRAP-related protein FRP1) protein.

L17 ANSWER 4 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
AN ABP97119 Protein DGENE
AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence represents human **p53** which is given in the exemplification of the present invention.
ACCESSION NUMBER: ABP97119 Protein DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N) KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
CROSS REFERENCES: N-PSDB: ACC49400
DESCRIPTION: Human **p53** protein.

L17 ANSWER 5 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -

AN ABP97118 Protein DGENE
AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence represents human **ATM** which is given in the exemplification of the present invention.

ACCESSION NUMBER: ABP97118 Protein DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N) KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
CROSS REFERENCES: N-PSDB: ACC49399
DESCRIPTION: Human **ATM** protein.

L17 ANSWER 6 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
AN ACC49416 DNA DGENE
AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV).

ATM has anti-HIV, cytostatic, antipsoriatic and antitumour activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence represents an oligonucleotide which is given in the exemplification of the present invention.

ACCESSION NUMBER: ACC49416 DNA DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N) KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
DESCRIPTION: Human **ATM** related oligonucleotide #14.

L17 ANSWER 7 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
AN ACC49415 DNA DGENE
AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the

cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence represents an oligonucleotide which is given in the exemplification of the present invention.

ACCESSION NUMBER: ACC49415 DNA DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N)KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
DESCRIPTION: Human **ATM** related oligonucleotide #13.

L17 ANSWER 8 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
AN ACC49414 DNA DGENE
AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence represents an oligonucleotide which is given in the exemplification of the present invention.

ACCESSION NUMBER: ACC49414 DNA DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N)KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p

APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
DESCRIPTION: Human **ATM** related oligonucleotide #12.

L17 ANSWER 9 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
AN ACC49413 DNA DGENE
AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence represents an oligonucleotide which is given in the exemplification of the present invention.
ACCESSION NUMBER: ACC49413 DNA DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N) KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
DESCRIPTION: Human **ATM** related oligonucleotide #11.

L17 ANSWER 10 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -

AN ACC49412 DNA DGENE
AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence represents an oligonucleotide which is given in the exemplification of the present invention.
ACCESSION NUMBER: ACC49412 DNA DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N) KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
DESCRIPTION: Human **ATM** related oligonucleotide #10.

L17 ANSWER 11 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
AN ACC49411 DNA DGENE
AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour

activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence represents an oligonucleotide which is given in the exemplification of the present invention.

ACCESSION NUMBER: ACC49411 DNA DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N) KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
DESCRIPTION: Human **ATM** related oligonucleotide #9.

L17 ANSWER 12 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
AN ACC49410 DNA DGENE
AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as

adjuncts in cancer radiotherapy and chemotherapy. The present sequence represents an oligonucleotide which is given in the exemplification of the present invention.

ACCESSION NUMBER: ACC49410 DNA DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N)KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
DESCRIPTION: Human **ATM** related oligonucleotide #8.

L17 ANSWER 13 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
AN ACC49409 DNA DGENE
AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence represents an oligonucleotide which is given in the exemplification of the present invention.

ACCESSION NUMBER: ACC49409 DNA DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N)KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821

PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
DESCRIPTION: Human **ATM** related oligonucleotide #7.

L17 ANSWER 14 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
AN ACC49408 DNA DGENE
AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence represents an oligonucleotide which is given in the exemplification of the present invention.
ACCESSION NUMBER: ACC49408 DNA DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N)KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
DESCRIPTION: Human **ATM** related oligonucleotide #6.

L17 ANSWER 15 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
AN ACC49407 DNA DGENE

AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence represents an oligonucleotide which is given in the exemplification of the present invention.

ACCESSION NUMBER: ACC49407 DNA DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N)KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
DESCRIPTION: Human **ATM** related oligonucleotide #5.

L17 ANSWER 16 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
AN ACC49406 DNA DGENE
AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour activities. M1 is useful for assaying for a compound able to affect DNA

binding by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence represents an oligonucleotide which is given in the exemplification of the present invention.

ACCESSION NUMBER: ACC49406 DNA DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N)KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
DESCRIPTION: Human **ATM** related oligonucleotide #4.

L17 ANSWER 17 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
AN ACC49405 DNA DGENE
AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence

represents an oligonucleotide which is given in the exemplification of the present invention.

ACCESSION NUMBER: ACC49405 DNA DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N)KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
DESCRIPTION: Human **ATM** related oligonucleotide #3.

L17 ANSWER 18 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
AN ACC49404 DNA DGENE
AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence represents an oligonucleotide which is given in the exemplification of the present invention.

ACCESSION NUMBER: ACC49404 DNA DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N)KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716

GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
DESCRIPTION: Human **ATM** related oligonucleotide #2.

L17 ANSWER 19 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
AN ACC49403 DNA DGENE
AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence represents an oligonucleotide which is given in the exemplification of the present invention.
ACCESSION NUMBER: ACC49403 DNA DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N) KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
DESCRIPTION: Human **ATM** related oligonucleotide #1.

L17 ANSWER 20 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
AN ACC49402 cDNA DGENE
AB The present invention describes an **assay** (M1) for a compound

able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence encodes human DNA dependent protein kinase catalytic subunit (DNA-PKcs) which is given in the exemplification of the present invention.

ACCESSION NUMBER: ACC49402 cDNA DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N) KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
CROSS REFERENCES: P-PSDB: ABP97121
DESCRIPTION: Human DNA dependent protein kinase catalytic subunit encoding cDNA.

L17 ANSWER 21 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
AN ACC49401 cDNA DGENE
AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour

activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence encodes human ATR (also known as FRAP-related protein FRP1) which is given in the exemplification of the present invention.

ACCESSION NUMBER: ACC49401 cDNA DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N) KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
CROSS REFERENCES: P-PSDB: ABP97120
DESCRIPTION: Human ATR (FRAP-related protein FRP1) encoding cDNA.

L17 ANSWER 22 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
AN ACC49400 cDNA DGENE
AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the

cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence encodes human **p53** which is given in the exemplification of the present invention.

ACCESSION NUMBER: ACC49400 cDNA DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N)KUDOS PHARM LTD.
PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
CROSS REFERENCES: P-PSDB: ABP97119
DESCRIPTION: Human **p53** encoding cDNA.

L17 ANSWER 23 OF 24 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
AN ACC49399 cDNA DGENE
AB The present invention describes an **assay** (M1) for a compound able to affect DNA **binding** by an ataxia-telangiectasia mutated (**ATM**) protein or a protein having an associated kinase activity. M1 comprises bringing into contact a substance which is **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound. Also described: (1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1; (2) purifying (M2) **ATM** or related kinase such as ATR; (3) use of DNA (II) for purifying **ATM** or ATR; and (4) a substantially pure **ATM** (III) or ATR (IV). **ATM** has anti-HIV, cytostatic, antipsoriatic and antitumour activities. M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR. (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumours, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts in cancer radiotherapy and chemotherapy. The present sequence encodes human **ATM** which is given in the exemplification of the present invention.

ACCESSION NUMBER: ACC49399 cDNA DGENE
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA -
INVENTOR: Jackson S P; Lakin N D; Smith G C M
PATENT ASSIGNEE: (KUDO-N)KUDOS PHARM LTD.

PATENT INFO: GB 2362952 A 20011205 129p
APPLICATION INFO: GB 2001-20368 20010821
PRIORITY INFO: GB 1997-14971 19970716
GB 1998-15423 19980716
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2003-232383 [23]
CROSS REFERENCES: P-PSDB: ABP97118
DESCRIPTION: Human **ATM** encoding cDNA.

L17 ANSWER 24 OF 24 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
TI **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA.
AN 2003-232383 [23] WPIDS
CR 1999-073587 [07]
AB GB 2362952 A UPAB: 20030428
NOVELTY - **Assay** (M1) for a compound able to affect DNA **binding** by ataxia-telangiectasia mutated (**ATM**) gene or a protein having an associated kinase activity,comprising bringing into contact **ATM** or a protein having an associated kinase activity which is able to bind DNA and a test compound, and determining **binding** of **ATM** and DNA in the presence of the test compound, is new.

DETAILED DESCRIPTION - **Assay** (M1) for a compound able to affect DNA **binding** by ataxia-telangiectasia mutated (**ATM**) gene or a protein having an associated kinase activity, involves bringing into contact a substance which is **ATM** or a protein having an associated kinase activity, or its fragment, variant or derivative which is able to bind DNA and a test compound, under conditions, where in the absence of the test compound being an **inhibitor** of DNA **binding** by **ATM** or the protein having an associated kinase activity, the substance binds DNA, and determining **binding** between the substance and the DNA.

INDEPENDENT CLAIMS are also included for the following:

(1) an agent (I) capable of affecting DNA **binding** by **ATM** obtained using M1;

(2) purifying (M2) **ATM** or related kinase such as ATR, by contacting a mixture of molecules including **ATM** or ATR with DNA or n-(5-amino-1-carboxypentyl)imino-diacetic acid (NTA), washing molecules which do not bind a DNA or NTA, and recovering **ATM** or ATR from the DNA- or NTA-bound fraction;

(3) use of DNA (II) for purifying **ATM** or ATR; and

(4) a substantially pure **ATM** (III) or ATR (IV).

ACTIVITY - Anti-HIV; Cytostatic; Antipsoriatic; Antitumor. No biological dats is given.

MECHANISM OF ACTION - Modulator of **ATM** (claimed); Regulator of immune system function; **Inhibitor** of cell proliferation; Modulator of interaction of **ATM** with **p53** protein. No supporting data is given.

USE - M1 is useful for assaying for a compound able to affect DNA **binding** by **ATM** or a protein having an associated kinase activity. (I) is useful in therapy involving modulating **ATM** action or in the manufacture of a medicament for modulating **ATM** action. (II) is useful for purifying **ATM** or ATR (all claimed). (I) is also useful for treating humans with ataxia-telangiectasia, AIDS or cancer, for treating or preventing disease states associated with premature and normal aging for regulating immune system function, for **inhibiting** cell proliferation by activating cell cycle check point arrest in the absence of cellular damage, which may be used in the treatment of tumors, cancer, psoriasis and other hyperproliferative disorders, for activating **p53** in cells without damaging the cells, for augmenting cancer radiotherapy and chemotherapy, or as adjuncts

in cancer radiotherapy and chemotherapy.
Dwg.0/11

ACCESSION NUMBER: 2003-232383 [23] WPIDS
CROSS REFERENCE: 1999-073587 [07]
DOC. NO. CPI: C2003-059869
TITLE: **Assay** for compound affecting DNA **binding** by ataxia-telangiectasia mutated gene, by bringing into contact the gene, protein with kinase activity, DNA and test compound, and determining **binding** of the gene and DNA.
DERWENT CLASS: B04 D16
INVENTOR(S): JACKSON, S P; LAKIN, N D; SMITH, G C M
PATENT ASSIGNEE(S): (KUDO-N) KUDOS PHARM LTD
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
GB 2362952	A	20011205	(200323)*		129
GB 2362952	B	20020306	(200326)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
GB 2362952	A	Derived from	GB 1998-15423	19980716
			GB 2001-20368	20010821
GB 2362952	B	Derived from	GB 1998-15423	19980716
			GB 2001-20368	20010821

PRIORITY APPLN. INFO: GB 1997-14971 19970716